Table S1. Study Characteristics and Key Findings*

Author(s) (Year)	Title	Country	Study type/intervention (if applicable)	Measurement	Setting/Sample	Key findings, including N analyzed if different from N in sample**
Bhowmik et al. (2005) (1)	Effects of exacerbations and seasonality on exhaled nitric oxide in COPD	UK	Prospective cohort study	F_{ENO} was measured using a chemiluminescence analyzer (Model LR 2000; Logan Research, Rochester, UK).	N=98, COPD patients included in this study were volunteers from the outpatient clinics at the London Chest Hospital (London, UK).	N=79 (Nineteen patients could not perform an adequate baseline exhalation: they were older and with lower FEV1 and FVC) Lower F_{ENO} in current smokers than non-smokers. No association between F_{ENO} with FEV1, FVC or exacerbation frequency No significant difference between patients who took ICS and/or inhaled long-acting beta-agonist and who not (n=8, n=19 respectively) Higher level of F_{ENO} from October to December perhaps due to viral infection Higher levels of F_{ENO} in exacerbation, N=38
Foschino Barbaro et al. (2007) (2)	Inflammation, oxidative stress and systemic effects in mild chronic obstructive pulmonary disease	Italy	Not mentioned	F_{ENO45} was measured using a rapid-response chemiluminescence NO analyzer (model 280; Sievers Instruments; Boulder, Colorado, USA).	N=27 mild stable ex-smoker COPD, N=15 healthy smoker were recruited from the Respiratory Disease Institute, University of Foggia.	Higher F_{ENO45} in COPD patients compared to control subjects and in reversible compared to non-reversible COPD COPD patients with airway reversibility showed increased sputum eosinophils and exhaled NO
Liu et al. (2007) (3)	Nitric Oxide and Exhaled Breath Nitrite/Nitrates in Chronic	Australia	Cross-sectional	F_{ENO} was measured offline by using a closed circuit which was connected to a	N=96 COPD and N=80 healthy subjects were recruited from the community,	No effect of smoking status (even in control group) or glucocorticosteroid (GCS) treatment on F_{ENO} levels in COPD patients

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	Obstructive Pulmonary Disease Patients			chemiluminescent NO analyzer for NO determinations (Dasibi Environmental Corp., Glendale, Calif., USA).	including hospital staff and their friends, and the respiratory outpatient clinics of the Prince of Wales Hospital and St. Vincent's Hospital.	Higher F_{ENO} levels in COPD patients than normal subjects
de Laurentiis et al. (2008) (4)	Exhaled nitric oxide monitoring in COPD using a portable analyzer	Italy	Cohort, Prospective	F_{ENO50} was measured using electrochemical F_{ENO50} device (NIOX MINO, Aerocrine, Sweden) and the chemiluminescence analyzer (NOA, Sensormedics, Italy).	N=59 COPD patients visiting department as outpatients	Higher mean coefficient of variability (CoV) F_{ENO50} in COPD than healthy group Lower F_{ENO50} levels in COPD current smokers than COPD ex-smoker No association between F_{ENO50} and FEV1 Significant association between individual exacerbations and F_{ENO50}
Kunisaki et al. (2008) (5)	Exhaled nitric oxide, systemic inflammation, and the spirometric response to inhaled fluticasone propionate in severe chronic obstructive pulmonary disease: A prospective study	USA	A single-arm, open-label prospective study/Salmeterol, fluticasone propionate	F_{ENO50} was measured online (real-time) with a chemiluminescence device (Sievers NOA 280i, GE Analytical Instruments, Boulder, CO).	N=73 ex-smoker severe COPD were recruited from the Minneapolis Veterans Affairs Medical Center.	N=60 (Thirteen subjects were withdrawn: they were similar in COPD severity but used more medications (antibiotics, prednisolone, inhaled corticosteroid before study participation)). No association between baseline (pre-ICS) F_{ENO50} with FEV1 or FVC F F_{ENO50} significantly decreased after four weeks of ICS therapy. Significant difference in baseline F_{ENO50} levels between ICS responders and non-responders, higher baseline F_{ENO50} levels compared with non-responders

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Beg et al. (2009) (6)	Exhaled Nitric Oxide in Chronic Obstructive Pulmonary Disease	Saudi Arabia	Cross-sectional	F_{ENO50} was measured using NOX EVA 4000 chemiluminescence analyzer (SERES-FRANCE).	N=14 COPD ex-smokers, N=25 patients with bronchial/naïve steroid asthma, and N=25 healthy recruited from pulmonary clinic at the King Khalid University Hospital, Riyadh, Saudi Arabia.	Significant higher F_{ENO50} in COPD patients than healthy Negative association between FEV1/FVC and the F_{ENO50} levels among COPD patients
Roy et al. (2009) (7)	COPD phenotype description using principal components analysis	UK	Single study visit	F_{ENO50} was measured using Niox chemiluminescence on-line analyzer (Aerocrine, Solna, Sweden).	N=127 COPD patients were recruited from primary care by media advertising.	Significant association between F_{ENO50} and sputum eosinophils, regardless of whether the data were expressed as percentage differential or cell count. Lower levels of F_{ENO50} in COPD smokers and women
Dummer et al. (2009) (8)	Predicting Corticosteroid Response in Chronic Obstructive Pulmonary Disease Using Exhaled Nitric Oxide	New Zealand	Randomized double-blind, placebo-controlled, crossover trial/ Oral Prednisone	F_{ENO50} was measured using an on-line chemiluminescence analyzer (Aerocrine AB, Solna, Sweden).	N=82 COPD patients were recruited from the research database and respiratory clinics.	N=62 (Thirteen patients were symptomatic after withdrawal of ICS, 2 had a too busy schedule to continue, 1 performed inadequate F_{ENO50} technique, and 1 had an unrelated illness, 2 patients were excluded because of nonadherence and 1 was excluded because of a new diagnosis of angina). F_{ENO50} decreased after prednisone in the case group. A significant association between off-steroid F_{ENO50} and sputum eosinophil percentage.

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						Significant association between baseline F_{ENO50} and the FEV1 A significant improvement in FEV1 from the lowest to the highest F_{ENO50} tertile There was a significant predictive value of baseline F_{ENO50} for an increase of 0.2 L in FEV1 with prednisone with an optimum F_{ENO50} cut-point of 50 ppb, area under the curve (AUC) 0.69, sensitivity 29%, and specificity 96%).
Antus et al. (2010) (9)	Relationship between exhaled nitric oxide and treatment response in COPD patients with exacerbation	Hungary	Longitudinal study	F_{ENO50} was measured using a chemiluminescence analyzer (Model LR2000, Logan Research, Rochester, UK).	N=58 COPD patients with exacerbations referred to the 3rd Pulmonary Department at National Koranyi Institute for TB and Pulmonology were recruited.	Lower F_{ENO50} levels in smokers at admission compared with ex-smokers Reduced F_{ENO50} levels in patients receiving ICS therapy compared with those not taking ICS at admission Similar F_{ENO50} level in men and women Significant positive association between F_{ENO50} levels at admission and the post-treatment increases in FEV1 and FEV1% predicted No association between an increase in FVC and F_{ENO50} levels at admission or with changes in F_{ENO50} levels F_{ENO50} was a good anticipator of a significant post-treatment increase in FEV1. The optimum cut point for F_{ENO50}

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						was 26.8 ppb with the sensitivity and specificity of 74 and 75%, respectively with the area under the ROC curve of 0.82. FEV1 and FEV1% predicted increased significantly at discharge in the group with high F_{ENO50} levels (> 26.8 ppb) (n = 24).
Lehouck et al. (2010) (10)	Alveolar and bronchial exhaled nitric oxide in chronic obstructive pulmonary disease	Belgium	Case-control	Exhaled NO was measured by a chemiluminescence analyzer (NIOX Flex; AerocrineAB, Stockholm, Sweden).	N=28 healthy ex-smokers, N=39 healthy smokers, N=55 COPD ex-smokers, and N=29 COPD smokers were recruited during the stable clinical conditions from the neighborhood Leuven(Belgium) via the service of Respiratory Medicine at the University Hospital of Leuven.	No significant difference in F_{ENO50} levels between COPD patients and age-matched healthy control Significant reduced F_{ENO50} in both current smoker COPD patients and healthy controls No significant difference in F_{ENO50} levels between the GOLD stages No significant association between FEV1 and F_{ENO50} No significant difference in F_{ENO50} and use of ICS (39% of COPD patients) No association between F_{ENO50} value measurements and age
Tilemann et al. (2011) (11)	Differences between local and systemic inflammatory markers in patients with obstructive airways disease	Germany	Not mentioned	F_{ENO50} was measured using a NioxMino® analyzer (Aerocrine AG, Solna, Sweden).	N=86 asthmatics, N=36 COPD, N=13 subjects with partial reversibility, and N=75 subjects with no obstructive airway diseases from adults presenting to their general practitioners	Higher level of F_{ENO50} in current non-smokers (never smokers and ex-smokers) than in current smokers Significant lower level of F_{ENO50} in COPD patients compared to subjects with no airway obstruction Association between F_{ENO50} with blood eosinophils and IgE levels

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					for the first time with complaints suggestive of obstructive airway disease were consecutively included.	
Rouhos et al. (2011) (12)	Repeatability of exhaled nitric oxide measurements in patients with COPD	Finland	Not mentioned	F_{ENO50} was measured using chemiluminescence analyzer (Sievers 270B, Boulder, CO, USA) by using computer software specially developed for this purpose.	N=20 COPD patients were recruited from the outpatient department of the Division of Respiratory Diseases and from the Research Unit for Respiratory Diseases of the Helsinki University Central Hospital, N=20 healthy subjects were recruited from the hospital staff and their relatives.	N=19 COPD (One subject was unable to perform acceptable F_{ENO50} measure), N=18 for F_{ENO} measurement (one subject did not return for second study day). Higher F_{ENO50} at baseline in COPD patients than healthy subjects Higher F_{ENO50} in both COPD and healthy subjects when the subjects did not use sodium bicarbonate
Bazeghi et al. (2011) (13)	Exhaled nitric oxide measure using multiple flows in clinically relevant subgroups of COPD	Denmark	Cohort database study, ECLIPES substudy	F_{ENO} was measured using a Niox chemiluminescence online analyzer (Aerocrine, Solna, Sweden).	N=91 COPD recruited for the ECLIPSE study. (ECLIPSE sub-study, using data of ECLIPSE database).	Significant lower F_{ENO} levels in active smokers than in ex-smokers
Akamatsu et al. (2011) (14)	Improvement of air flow limitation by	Japan	Not mentioned/ Fluticasone (FP), Salmeterol (SAL)	F_{ENO50} was measured using a chemiluminescence	N=14 stable COPD patients receiving long-acting	Significant decrease in F_{ENO50} levels by the treatment with FP/SAL No association between the baseline

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	fluticasone propionate/salmeterol in chronic obstructive pulmonary disease: what is the specific marker?			analyzer (modified NA-623N®; Chest, Inc., Tokyo, Japan).	muscarinic receptor antagonist(tiotropium 18μg/day) were consecutively enrolled from the outpatient clinic of Wakayama Medical University Hospital.	F_{ENO50} level and the changes in FEV1 as well as other pulmonary physiological parameters To identify subjects with significant improvement in FEV1, a baseline F_{ENO50} level >35 ppb is useful with the sensitivity of 80 and specificity of 66.7%. Improvement in FEV1 by adding treatment of FP/SAL in COPD subjects with F_{ENO50} >35 ppb
Antus et al. (2013) (15)	Relationship between exhaled nitric oxide and the frequency of severe acute exacerbation of COPD: 3-year follow-up	Hungary	Retrospective pilot study	Levels of F_{ENO50} were recorded using a chemiluminescence analyzer (Model LR2000, Logan Research Rochester, UK) at hospital admission.	N=58 COPD patients referred to the National Korányi Institute of TB and Pulmonology with an acute exacerbation of the disease were recruited.	No association between F_{ENO50} and inhaled corticosteroid (ICS), long-acting β2-agonist (LABA) and long-acting muscarinic agonist (LAMA) therapy on F_{ENO50} More exacerbations in COPD patients with low F_{ENO50} level Administrating antibiotics 18% more frequently in COPD subjects with low F_{ENO50} level than subjects in the high F_{ENO50} level group
Soter et al. (2013) (16)	Predicting Sputum Eosinophilia in Exacerbations of COPD using Exhaled Nitric Oxide	Hungary	Prospective study	F_{ENO50} was measured using a chemiluminescence analyzer (Model LR2500, Logan Research, Rochester, UK).	N=49 COPD patients referred to the National Koranyi Institute of TB and Pulmonology with an acute exacerbation of the disease were recruited consecutively for the study.	F_{ENO50} cut point: 26.8 parts per billion (ppb) was used for the estimation of the treatment response. Patients with F_{ENO50} levels of >26.8 ppb had a greater increase in FEV1 compared to those with F_{ENO50} levels of <26.8 ppb at admission Significant association between the percentage/number of sputum eosinophils and F_{ENO50} levels, both at

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						exacerbation and discharge To identify sputum eosinophilia in COPD patients with acute exacerbations, the optimum cut point of 19 ppb with AUC of 0.089 and sensitivity of 90% and specificity of 74% is useful.
Donohue et al. (2014) (17)	Characterization of airway inflammation in patients with COPD using fractional exhaled nitric oxide levels: a pilot study	USA	A pilot, observational (no treatment allocation), multicenter, single-visit	F_{ENO50} was measured using F_{ENO50} analyzer (NIOX MINO®; AerocrineAB).	N=200 COPD outpatients aged 40 years and older were recruited at two sites within the University of North Carolina, Chapel Hill, North Carolina, Department of Respiratory and Critical Care Medicine.	N=191(Nine patients were excluded due to inability to perform F_{ENO50} and/or spirometry or having asthma without COPD). Increased F_{ENO50} level in COPD patients No association between F_{ENO50} levels and GOLD stages (I-IV)
Xia et al. (2014) (18)	Fractional exhaled nitric oxide in bronchial inflammatory lung diseases	China	Not mentioned	F_{ENO50} was measured using SV-02 NO Instrument made in Wuxi Shangwo Biological Technology Co., Ltd.	N=38 COPD, N=57 suspected asthmatics, N=26 healthy subjects were recruited from those who had an outpatient visit at Central South University, Xiangya Hospital.	Significant higher level of F_{ENO50} in COPD patients than healthy subjects Significant higher level of F_{ENO50} in COPD patients with exacerbations (N=25) compared to stable COPD subjects (N=13) No association between F_{ENO50} with FEV1 and FEV1/FVC level in COPD patients Higher F_{ENO50} levels in smoking group (N=29) than non-smoker (N=34) (Mix subjects: stable COPD (N=13), healthy (N=26), non-asthmatic (N=24)

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Rawy et al. (2015) (19)	Fraction of exhaled nitric oxide measurement as a biomarker in asthma and COPD compared with local and systemic inflammatory markers	Egypt	Not mentioned	F_{ENO50} was measured using Niox Mino analyzer (Aerocrine AG, Solna, Sweden).	N=60 COPD, N=90 asthmatic, and N=30 control group with no airway obstruction were recruited from attended the pulmonary outpatient clinic.	Positive association between F_{ENO50} with sputum and blood eosinophil percentage Negative association between F_{ENO50} and age No association between F_{ENO50} and FEV1/FVC
Tamada et al. (2015) (20)	Biomarker-based detection of asthma-COPD overlap syndrome in COPD populations	Japan	Multicenter, cross-sectional study	F_{ENO50} was measured using the NIOX MINO® device (Aerocrine, Morrisville, NC, USA).	N=331 COPD outpatients were enrolled from Tohoku University Hospital, Sendai, Japan, and five hospitals (Tohoku University Hospital, Sendai, Japan; NTT East Tohoku Hospital, Sendai, Japan; Wakayama Medical University Hospital, Kimiidera, Japan; Hiraka General Hospital, Yokote, Japan; Iwate Prefectural Isawa Hospital, Oshu, Japan).	High F_{ENO50} in COPD with asthma-like airway inflammation (ACO) among COPD patients No association between low ($\leq$ 35 ppb) and high F_{ENO50} (> 35 ppb) levels with pulmonary function tests (FVC, FEV1, and FEV1/FVC). No association between high and low F_{ENO50} levels with GOLD stages (I-IV)
Durmaz et al.	The role of	Turkey	Prospective cohort study	F_{nNO5} was measured	N=92 COPD patients	No significant difference in F_{nNO5}

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(2015) (21)†	nitric oxide in predicting revisit of patients with exacerbated chronic obstructive pulmonary disease			using a hand-held analyzer device (NIOX MINO, Aerocrine, Solna, Sweden).	presented to the emergency department for the treatment of acute exacerbation	level at presentation or before discharge between the groups
Ishiura et al. (2015) (22)	A comparison of the efficacy of once-daily fluticasone furoate (FF)/ vilanterol (VI) with twice-daily fluticasone propionate (FP)/salmeterol (SAL) in asthma-COPD overlap syndrome	Japan	Randomized, open-label cross-over study/ fluticasone furoate(FF)/vilanterole (VI), fluticasone propionate (FP)	F_{ENO50} was measured using NIOX MINO™, Aerocrine, Stockholm, Sweden.	N=16 stable ACO	No significant difference in F_{ENO50} levels, among the run-in, FP/SAL treatment, and FF/VI treatment periods
Chou et al. (2015) (23)	Exhaled Nitric Oxide Predicts Eosinophilic Airway Inflammation in COPD	Taiwan	Not mentioned	F_{ENO50} levels were measured using hand-held analyzer (NIOX MINO, Aerocrine).	N=90 COPD were enrolled from outpatient clinics in Taipei Veterans General Hospital, a tertiary medical center and a university-affiliated teaching hospital in Taiwan.	Higher levels of F_{ENO50} in patients with sputum eosinophilia (N=29) compared to those without eosinophilia (N=61) Significant association between levels of sputum eosinophils, F_{ENO50}, and serum IgE in the COPD patients To predict sputum eosinophilia, use of F_{ENO50} at the cut-off of 23.5 ppb

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						with a sensitivity of 62.1 % and a specificity of 70.5 % is useful.
Santini et al. (2016) (24)	Exhaled and non-exhaled non-invasive markers for assessment of respiratory inflammation in patients with stable COPD and healthy smokers	Italy	Multicentre, observational, cross-sectional study	F_{ENO50} was measured with the NIOX system (Aerocrine, Stockholm, Sweden) with a single breath on-line method.	N=48 stable COPD ex-smokers, N=17 stable COPD current smokers, N=12 healthy current smokers, and N=12 healthy ex-smokers	N=47 stable COPD ex-smokers Lower F_{ENO50} levels in COPD current smokers compared to COPD ex-smokers Higher F_{ENO50} in COPD ex-smoker compared to healthy ex-smoker No difference in F_{ENO50} values between COPD patients on ICS therapy and those not on ICS therapy
Arif et al. (2016) (25)	Use of Exhaled Nitric Oxide as a Biomarker in Diagnosis and Management of Chronic Obstructive Pulmonary Disease	USA	Secondary data from the National Health and Nutrition Examination Survey 2007 to 2010	Not mentioned	N=10214 individuals 30 years or older from the National Health and Nutrition Examination	No association between F_{ENO50} and COPD or between COPD severity (GOLD stage I-IV) and F_{ENO50}
Alcazar-Navarrete et al. (2016) (26)	Diagnostic performance of the measurement of nitric oxide in exhaled air in the diagnosis of COPD phenotypes	Spain	Cross-sectional observational study	F_{ENO50} was measured using chemiluminescence analyzer of nitric oxide (HypAirFeNO®, Medisoft, Belgium)	N=103 COPD, N=16 healthy nonsmokers, N=30 healthy smokers, and N=43 asthmatics patients who received assistance consecutively in an outpatient pulmonary care facility were	Higher levels of F_{ENO50} in COPD than non-smoking healthy controls. No differences in F_{ENO50} levels between the GOLD 2011 groups Significant higher F_{ENO50} levels in ACO patients (N=22) than other COPD phenotypes (Non-exacerbators, N=34), frequent exacerbators with emphysema (N=13), frequent exacerbators with

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					enrolled.	chronic bronchitis (N=34)) To diagnose ACO, use of 19 ppb as the optimal cut off value of F_{ENO50} with a sensitivity of 0.68 and a, specificity of 0.75 and AUC of 0.79
Logotheti, et al. (2016) (27)	The role of exhaled nitric oxide in patients with chronic obstructive pulmonary disease undergoing laparotomy surgery-The noxious study	Greece	A prospective, observational study	F_{ENO50} measurement using a portable analyzer of nitric oxide (HypAir FeNO®, Medisoft, Belgium)	N=70 COPD smoker who were scheduled for major abdominal surgeries	Higher F_{ENO50} in older COPD patients compared to younger patients Lower F_{ENO50} in COPD patients under ICS than those who were not under ICS Association between GOLD category 2011 (ABCD) and the elevated F_{ENO50} Significant increase in exacerbations in COPD patients with elevated F_{ENO50} levels Association between elevated F_{ENO50} and extra hospital care
Amer, et al. (2016) (28)	Effect of Inhaled β2-Agonist on Exhaled Nitric Oxide in Chronic Obstructive Pulmonary Disease	New Zealand	Not mentioned/ Salbutamol (bronchodilator)	F_{ENO50} was measured using chemiluminescence nitric oxide analyzer (NOA 280i; Sievers, Boulder, CO)	N=24 stable COPD were recruited.	N=21 (Three subjects were not able to do acceptable maneuver). Increased level of F_{ENO50} in COPD subjects after bronchodilator therapy No association between the change in F_{ENO50} and change in FEV1.
Chen, et al. (2016) (29)	Importance of fractional exhaled nitric oxide in the differentiation	China	Not mentioned	F_{ENO50} was measured using a NO analyzer (NIOX MINO Analyzer; Aerocrine AB, Solna, Sweden)	N=132 COPD, N=500 asthmatics, and N=57 ACO visiting the First Affiliated Hospital of Sun Yet-Sen	Significant higher level of F_{ENO50} in ACO than COPD group No differences in F_{ENO50} levels among the GOLD groups (stage I-IV)

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	of asthma-COPD overlap syndrome, asthma, and COPD				University were retrospectively enrolled in this study.	To differentiate ACO from COPD, the optimal F_{ENO50} cut-off value was 22.5 ppb with 70% sensitivity and 75% specificity and AUC of 0.78.
Ji, et al. (2016) (30)	Fractional exhaled nitric oxide detection in treatment of asthma-chronic obstructive pulmonary disease overlap syndrome	China	Not mentioned/ ICS/LABA	F_{ENO50} was measured using NIOX MINO Aerocrine AB, Sweden	N=28 ACO and N=28 healthy subjects were recruited from Kowloon Hospital outpatient or ward.	Significant decrease in the level of F_{ENO50} among ACO subjects after treatment Higher level of F_{ENO50} in ACO group than healthy subjects both before and after treatment Positive association between pre and post-treatment F_{ENO50} levels with sputum eosinophils and serum total IgE No association between F_{ENO50} levels of pre and post treatment with FEV1% predicted
Goto, et al. (2016) (31)	Fractional exhaled nitric oxide levels in asthma–COPD overlap syndrome: analysis of the National Health and Nutrition Examination Survey, 2007–2012	USA	Cross-sectional analysis of the National Health and Nutrition Examination Survey (NHANES)	F_{ENO50} was measured using Aerocrine NIOX MINO ® (Aerocrine AB, Solna, Sweden).	Data of N=197 COPD patient from National Health and Nutrition Examination Survey (NHANES)	Higher levels of F_{ENO50} in subjects with ACO (N=48 from 197 COPD) compared to those with COPD alone
Huang, et al. (2016) (32)	Exercise-Induced	Taiwan	Control, prospective study	F_{ENO50} was measured by NIOX MINO	N=62 COPD, N=60 asthma, and N=27	Higher levels of F_{ENO50} were in COPD patients compared to healthy

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	Changes in Exhaled NO Differentiates Asthma With or Without Fixed Airway Obstruction From COPD With Dynamic Hyperinflation			(Aerocrine AB, Sweden), a hand-held device.	healthy subjects were recruited from outpatient clinics of Chang Gung Memorial Hospital, Linkuo Medical Center in Taiwan.	subjects at the baseline. Significant decrease in the change of F_{ENO50} level after 6MWT in patients with COPD No association between the percentage of F_{ENO50} change and the % predicted value of FEV1 at baseline or the percent change of FEV1 in COPD patients
Kobayashi, et al. (2016) (33)	Inflammatory biomarkers in asthma-COPD overlap syndrome	Japan	Cross-sectional study	F_{ENO50} level was measured using the NIOX MINO device (Aerocrin, Morrisville, NC, USA).	N=257 COPD patients, data were collected from prospectively consecutively scheduled visits or newly registered patients from the Ishinomaki COPD Network (ICON) registry.	Higher F_{ENO50} levels in ACO compared to non-ACO No association between F_{ENO50} levels and ICS therapy in neither ACO nor non-ACO group To diagnose ACO, the best cutoff value of F_{ENO50} was 23 ppb with AUC 0.74, the sensitivity of 73%, and specificity of 68.2%.
Feng et al. (2017) (34)	Relationship between Fractional Exhaled Nitric Oxide Level and Efficacy of Inhaled Corticosteroid in Asthma-COPD Overlap	China	Not mentioned/ ICS (budesonide inhalation suspension)	The F_{ENO50} levels were measured using a nitric oxide analyzer (Niox; Aerocrine AB, Solna, Sweden).	N=127 ACO and N=131 healthy subjects were enrolled.	Higher F_{ENO50} levels in ACO patients than healthy subjects at baseline (before ICS therapy) Decrease in F_{ENO50} levels in all ACO patients compared to pre-treatment levels after ICS therapy Positive association between F_{ENO50} levels with total serum IgE and sputum eosinophil Negative association between F_{ENO50}

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	Syndrome Patients with Different Disease Severity					levels with FEV1%pred and FEV1/FVC
Cosío, et al. (2017) (35)	Th-2 signature in chronic airway diseases: towards the extinction of Asthma-COPD overlap syndrome?	Spain	Cross-sectional, observational, multicentre study	Not mentioned	N=89 COPD, N=94 asthmatics, and N=109 ACO recruited from 23 outpatient clinics based in tertiary hospitals in Spain.	Higher F_{ENO50} in ACO than COPD No significant difference in F_{ENO50} between COPD subjects with eosinophilia and those without eosinophilia
Deng, et al. (2017) (36)	The value of fractionated exhaled nitric oxide in the diagnosis of asthma-chronic obstructive pulmonary disease overlap syndrome	China	Not mentioned	F_{ENO50} was measured using Naku Lun breath analyzer.	N=82 COPD, N=76 asthma, N=81 ACO, and N=39 healthy non-smoker subjects were recruited from those who had an outpatient visit at Central South University, Xiangya Hospital.	Higher F_{ENO50} levels in ACO patients than COPD patients No association between F_{ENO50} and FEV1% predicted and FEV1/FVC in COPD and ACO To differentiate ACO form COPD patients, the best cutoff value was 29 ppb with a sensitivity 80% and specificity 73%.
Gao et al. (2017) (37)	Correlation between fractional exhaled nitric oxide and sputum eosinophilia in exacerbations of COPD	China	Cross-sectional study	F_{ENO50} was measured using NO electrochemical equipment (NIOX Vero; Aerocrine AB, Solna, Sweden).	N=68 COPD patients diagnosed to have acute exacerbations visiting the Third People's Hospital of Guangzhou Medical College in Huizhou, China	Elevated F_{ENO50} levels in patients with sputum eosinophilia compared to patients without eosinophilia Significant association between sputum eosinophils and F_{ENO50} levels No significant association between F_{ENO50} levels and blood eosinophil ratio To diagnose sputum eosinophilia, the best F_{ENO50} cut-off value was 17.5

						ppb with a sensitivity of 64.5%, specificity of 56.4%, AUC 0.617.
Zhao, et al. (2017) (38)	Albuterol inhalation increases FeNO level in steroid-naive asthmatics but not COPD patients with reversibility	China	Observational, prospective study/ Albuterol (bronchodilator)	F_{ENO50} was measured using a portable nitric oxide analyzer (NIOX MINO; Aerocrine AB, Solna, Sweden).	N=30 steroid-naive asthma, N=25 ICS treated asthma, and N=20 COPD outpatients selected from patients at the Department of Respiratory Medicine at a hospital.	No significant change in F_{ENO50} after albuterol inhalation in COPD patients No significant associations between sputum eosinophils and F_{ENO50} levels both before and after bronchodilator inhalation No association between the F_{ENO50} and change in FEV1 after bronchodilator therapy

COPD: Chronic obstructive lung disease; UK: United Kingdom; F_{ENO}: Fractional exhaled nitric oxide; FEV1: Forced expiratory volume in first second; FVC: Forced vital capacity; ICS: Inhaled corticosteroid; USA: United States of America; GCS: Glucocorticoid, CoV: Coefficient of variation; AUC: Area under the curve; ROC: Receiver operative characteristics; ppb: parts per billion; GOLD: Global Initiative for Chronic Obstructive Lung Disease; BMI: Body mass index; IgE: Immunoglobulin E; FP: Fluticasone; SAL: Salmeterol; TB: Tuberculosis; LABA: Long-acting beta agonist; LAMA: Long-acting muscarinic antagonists; ACO: Asthma-COPD overlap; Fn_{NO}: Fractional concentration of nasally aspirated/exhaled nitric oxide; FF: Fluticasone furoate; VI: vilanterol; NHANES: National Health and Nutrition Examination Survey; 6MWT: 6-minute walk test; Th-2: T-helper 2

* for expressing the F_{ENO}, the exhalation flow rate (if indicated) was given as a subscript in $mL \cdot s^{-1}$. For instance, a flow rate of 50 $mL \cdot s^{-1}$ was written F_{ENO50}. If there was no direct or indirect evidence regarding the flow rate ($mL \cdot s^{-1}$), we only used $F_{ENO.}$ The title of articles was excepted from this rule.

**Concerning ACO definitions, the studies used the following definitions; a) One study (35) used this definition: previously diagnosed asthma patients with chronic airflow limitation and a smoking history ⩾20 pack-years, or a diagnosed COPD patients who have a blood eosinophil count ⩾200 eosinophils$\cdot \mu L^{-1}$, b) One study (26) defined ACO according to the validated major or minor criteria, if a subject has one of these major criteria, including previous history of asthma/wheezing outside chest infections or a documented very positive bronchodilator test (>14% and >400 mL increase in FEV1) or if a subject has two of these minor criteria, including blood eosinophil count >3%, IgE levels >100 UI/L, 2 documented positive bronchodilator test with >12% or 200 mL gain in FEV1, atopy or previous history sensibilization to neumoalergens

demonstrated by positive skin prick test or specific IgE to allergens, c) One study (29) defined ACO as bronchodilator test with 12% and 200 mL gain in FEV1, and presence of clinical characteristics of asthma (previous history of asthma/wheezing), d) Another study (31) defined ACO as self-reported wheezing in past 12 months plus bronchodilator response (FVC increase of 200 mL and 12%) or self-reported physician diagnosis of asthma, also in its sensitive analysis alternative definition of ACO was used which was defined by the presence of one major criterion or two minor criteria. Major criteria included history of asthma and bronchodilator response of ≥15% and 400 mL; minor criteria consisted of history of hay fever, bronchodilator responses to salbutamol of ≥12% and 200 mL, and blood eosinophils ≥5%, e) One study considered high levels of fractional exhaled nitric oxide (FENO > 35 ppb) or immunoglobulin E (IgE ≥ 173 IU/mL) in diagnosed COPD as markers of ACO candidate (20), f) One study (33) defined ACO according to the GINA-GOLD joint document (updated 2015) (39), g) One study (36) defined ACO according to the GINA-GOLD joint document 2014 (40). Sputum eosinophilia/elevated sputum eosinophils was defined as sputum eosinophil count ≥ 2.5% (37) or ≥ 3% (16) or > 3% (23) or no definition (2,7,8,11,19,30,34,35,38). Elevated blood eosinophils was defined as blood eosinophil count ≥ 1% (37) or ≥200 eosinophils·μL^{-1} (35) or no definition (11,19). Treatment response was defined as an increase in FEV1≥ 200mL (5) or > 200mL (14) or >12% and >200 mL (9,16). Treatment response was not defined in three studies (28,34,38). Concerning exacerbation definitions, the studies used the following definitions; a) event-based exacerbation was defined as the use of oral corticosteroids and/or antibiotics and/or hospitalization for a worsening in the patient's respiratory symptoms (4), b) exacerbation was defined as increased dyspnea, cough or sputum (quality or quantity) with a duration ≥3 days requiring treatment with antibiotics and/or systemic corticosteroids and/or a significant change in prescribed respiratory medication (15), c) exacerbation was defined as the demonstration of any combination of the following symptoms: purulence of sputum, increased dyspnea, or increased production of sputum (21), d) exacerbation was defined as the presence for ≥2 consecutive days of any two symptoms (''major'' symptoms was defined as dyspnoea, increased sputum purulence, increased sputum quantity or ''minor'' symptoms was defined as wheeze, sore throat, cough and symptoms of a common cold, which were defined as nasal congestion and/or nasal discharge), at least one of which must be a major symptom (1). Exacerbations were not defined in two studies (18,27).

† The flow rate of the nasally exhaled/aspirated nitric oxide (F_{nNO}) was given as a subscript in mL·s^{-1} (F_{nNO5}).

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