

FeNO in the Differential Diagnosis of Chronic Cough

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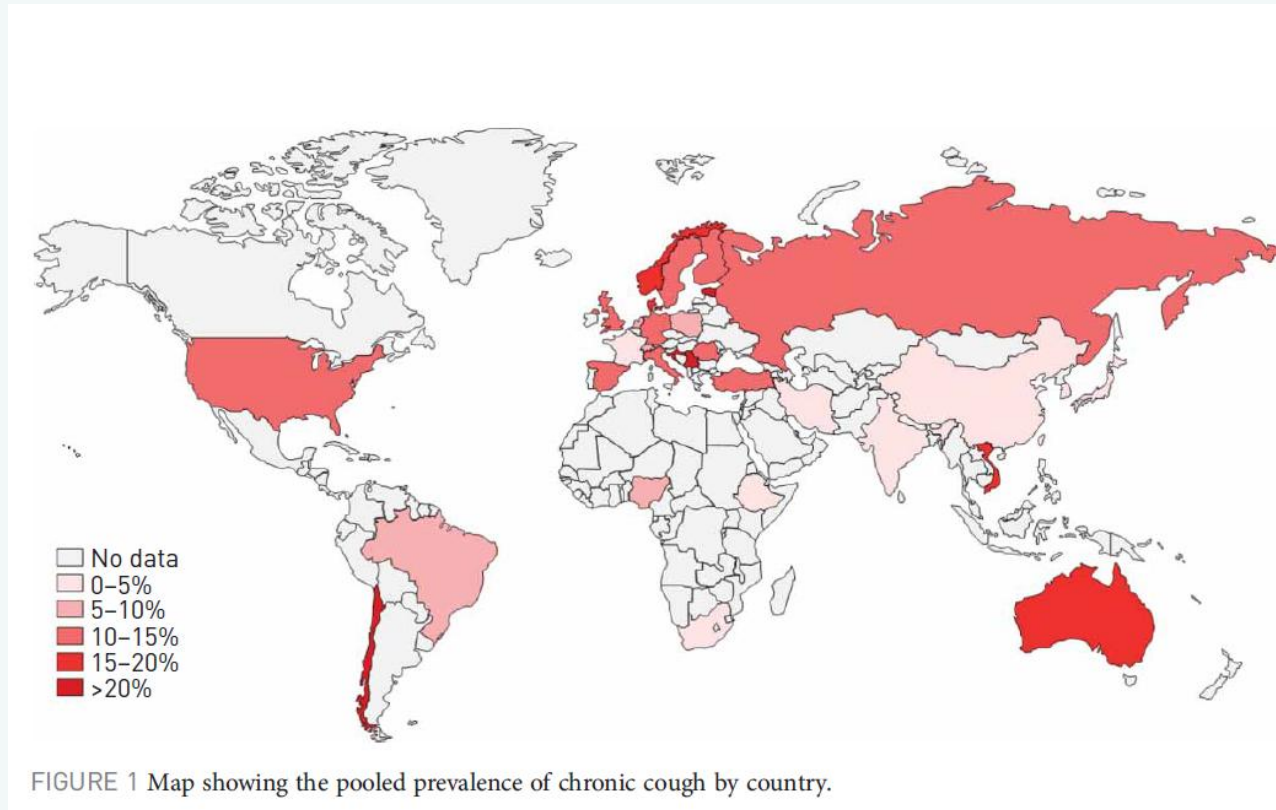
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Introduction



- Defined by **cough lasting more than 8 weeks** in adults
- Global prevalence of approximately 10%
- The United states (11.0%), and Europe (12.7%), Asia (4.4%), and Africa (2.3%)
- Impairs QoL, leading to physical complications, psychological distress, and social isolation

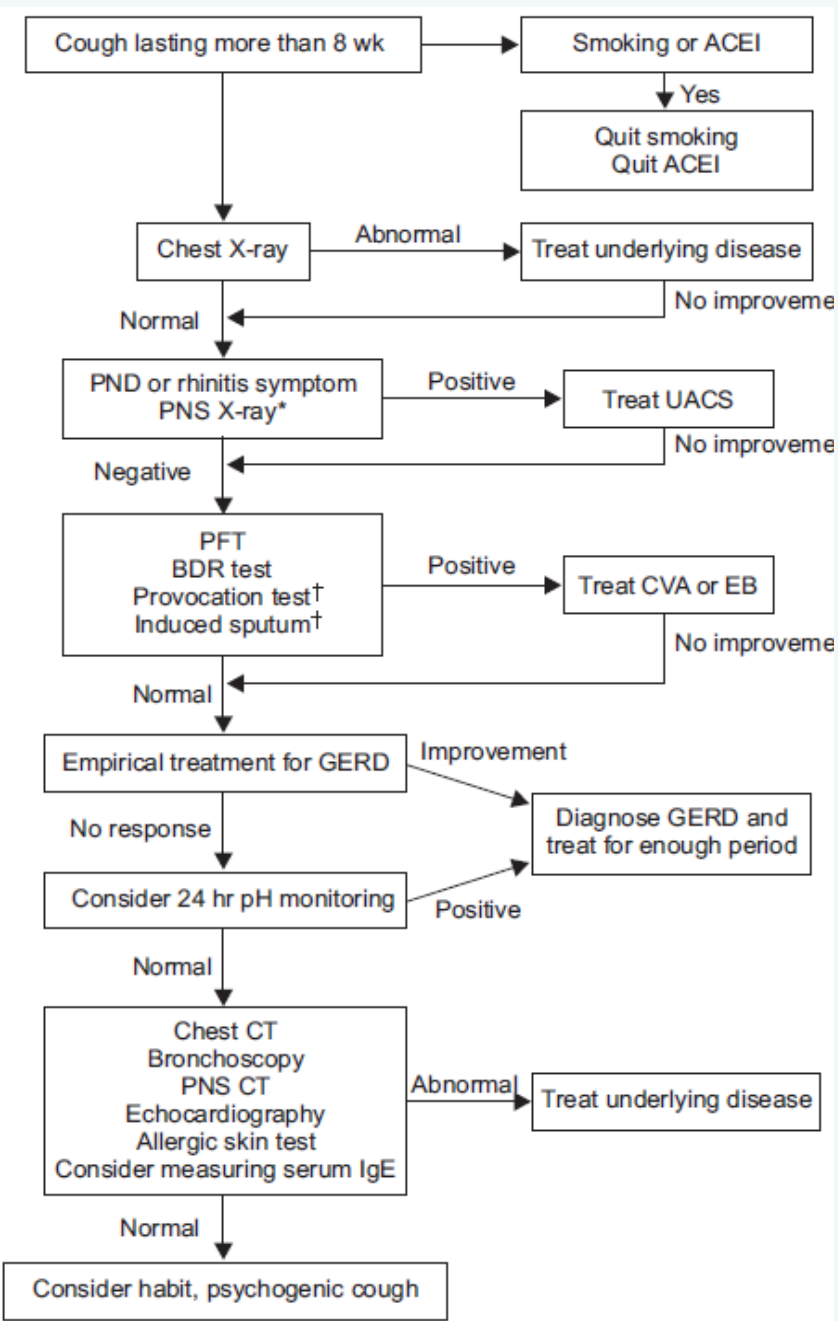
Introduction

Table 1. Baseline clinical characteristics of chronic cough in Korea

Characteristic	Value (n=427)
Age, yr	49.6±15.3
Male sex	106 (24.8)
Cough duration, wk	63.1±176.0
Cough NRS	
Baseline	5.3±1.6
After initial treatment	2.6±1.9
After 4 weeks treatment	1.2±1.4
Initial impression	
UACS	223 (52.2)
CVA	218 (51.1)
EB	29 (6.8)
GERD	56 (13.1)
Final diagnosis	
UACS	229 (53.6)
CVA	200 (46.8)
EB	34 (8.0)
GERD	63 (14.8)
Psychogenic cough	25 (5.9)
Others	12 (2.8)
Responder	
Initial	235 (63.3)
Final	321 (91.2)

Values are presented as mean±SD or number (%).
NRS: numeric rating scale; UACS: upper airway cough syndrome;
CVA: cough-variant asthma; EB: eosinophilic bronchitis; GERD: gastro-esophageal reflux disease; SD: standard deviation.

- **Mean duration of cough** : 63.1±176.0 weeks (more than 1-year)
- Survey reported the prevalence of chronic cough in the elderly to be **4.6%–9.3%** in Korea
- **UACS (53.6%)** was the most common cause, followed by **CVA (46.8%)**, GERD (14.8%), and EB (8.0%)
- Approximately **27.4%** of the patients had two or more causes of chronic cough



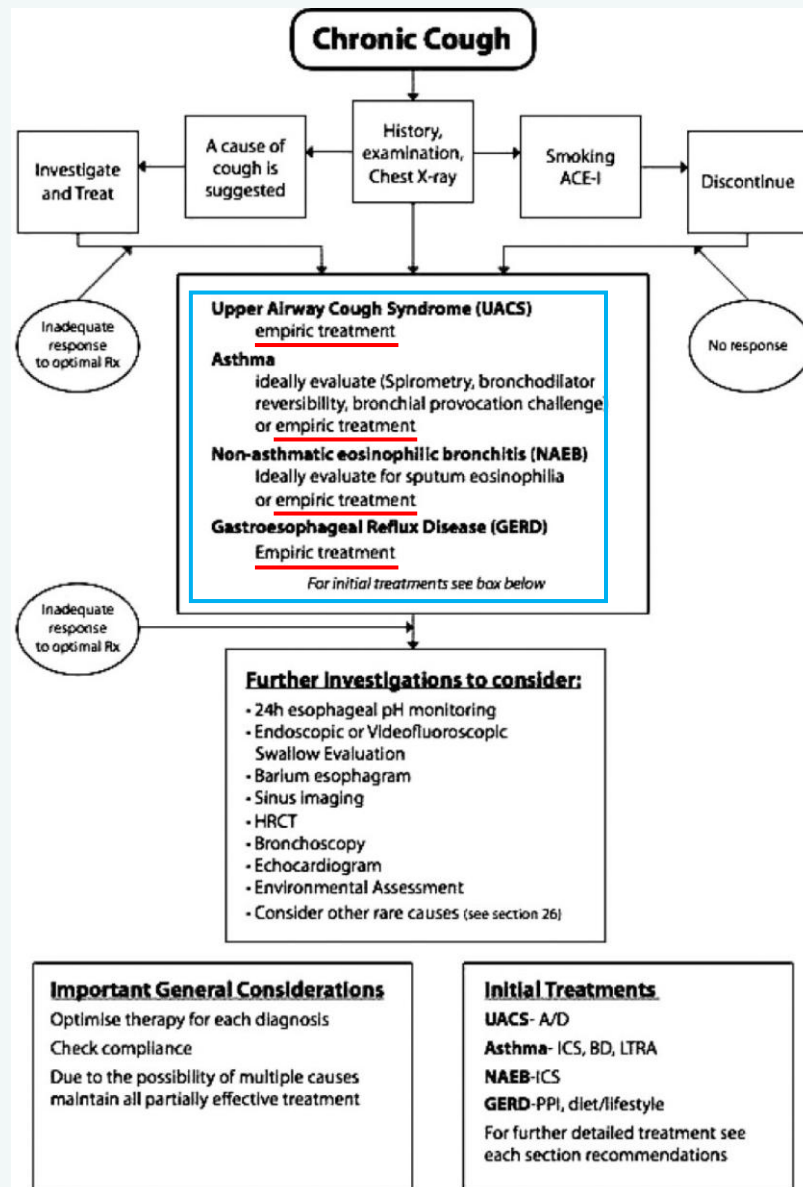
The Korean Cough Guideline

- When clinical manifestation is suspicious for UACS, **empirical treatment** can be tried even if PNS X-ray is normal.
- Empirical treatment can be considered when evaluation is not feasible.

Table 7. The medications used to treat chronic cough in Korea

UACS	Percentage	CVA	Percentage	EB	Percentage	GERD	Percentage
Antihistamine	66.2	ICS	4.2	ICS	46.2	Low-dose PPI	64.0
Nasal decongestant	1.0	ICS+LTRA	0.5	ICS+OCS	3.8	High-dose PPI	36.0
Antihistamine+ nasal decongestant	29.5	ICS/LABA	27.8	ICS/LABA	50.0		
Etc.	3.3	ICS/LABA+LTRA	38.7				
		ICS/LABA+OCS	2.1				
		ICS/LABA+LTRA+OCS	19.4				
		LTRA	3.1				
		OCS	2.1				
		OCS+LTRA	2.1				

Chronic cough: the conventional approach of diagnosis & treatment



Empirical treatment

- **UACS:** Antihistamine/decongestant
- **CVA & Asthma:** ICS, BD, LTRA
- **NAEB:** ICS
- **GERD:** PPI, Diet/lifestyle

Unmet needs in current practice

- Management relies largely on **sequential empirical treatment**
- Treatment response may be indistinguishable from spontaneous improvement
- **Empirical ICS** may expose patients without eosinophilic inflammation to unnecessary treatment
- Diagnosis is often made retrospectively, while induced sputum is not widely available
- **Biomarkers** may enable earlier identification of treatable traits

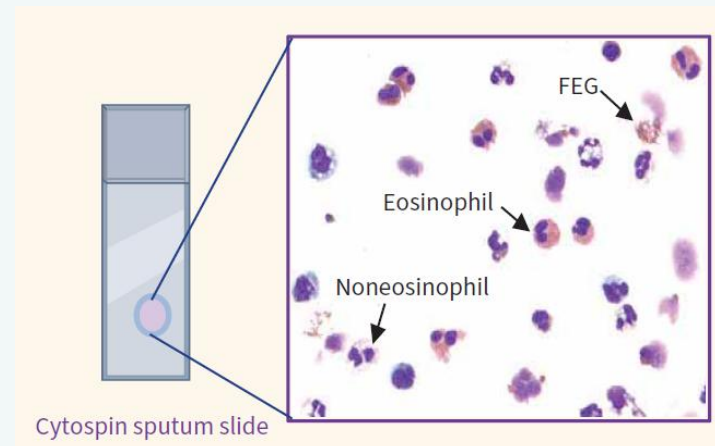
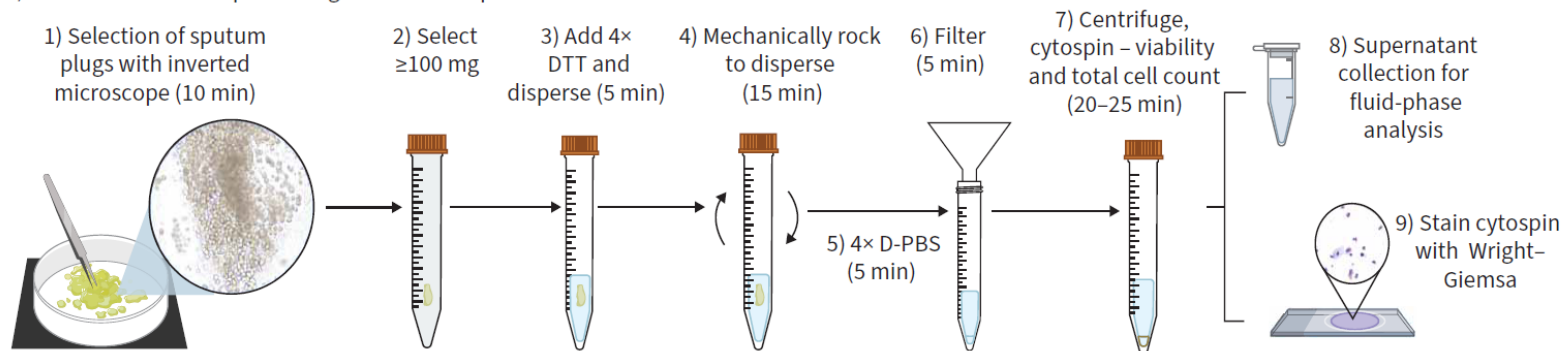
Pratter MR et al. Chest 2006;129:222S-31S
Rhee CK et al. Tuberc Respir Dis 2016;79:14-21
Irwin RS et al. Chest 2018;153:196-209
Lee JH et al. Allergy Asthma Immunol Res 2019;11:856-70
Haque RA et al. Chest 2005;127:1710-3
Gibson P et al. Chest 2016;149:27-44

Chronic cough: Three markers used to phenotype T2 inflammation

● Sputum eosinophils

- Gold standard for defining airway inflammatory phenotypes
- Direct, noninvasive method with high clinical relevance
- Sputum eosinophil count of >2-3%
- Technically demanding, time-consuming, prone to inter-observer variability
- Restricted to a small number of specialized institutions
- Patients may not produce enough sputum for analysis
- Limited in applicability despite high sensitivity & diagnostic accuracy

a) Routine clinical DTT processing: total time required ~1 h



Chronic cough: Three markers used to phenotype T2 inflammation

● Blood eosinophils

- Highly accessible compared with induced sputum
- ≥ 300 cells/ μ L is the accepted threshold for airway eosinophilia in asthma
- In chronic cough, blood eosinophils correlate strongly with FeNO ($r=0.79$; vs. $0.22-0.51$ in asthma cohorts) and modestly with sputum eosinophils ($r=0.59$)

● Limitations

- Highly variable over time — a single measurement cannot establish airway eosinophilia
- Most evidence comes from asthma, not cough populations
- Sputum-confirmed eosinophilic bronchitis does not always show blood eosinophilia
- Weak predictor of treatment response in an observational chronic cough cohort; no RCT evidence
- Useful and convenient, but not yet validated as a stand-alone guide to therapy in chronic cough

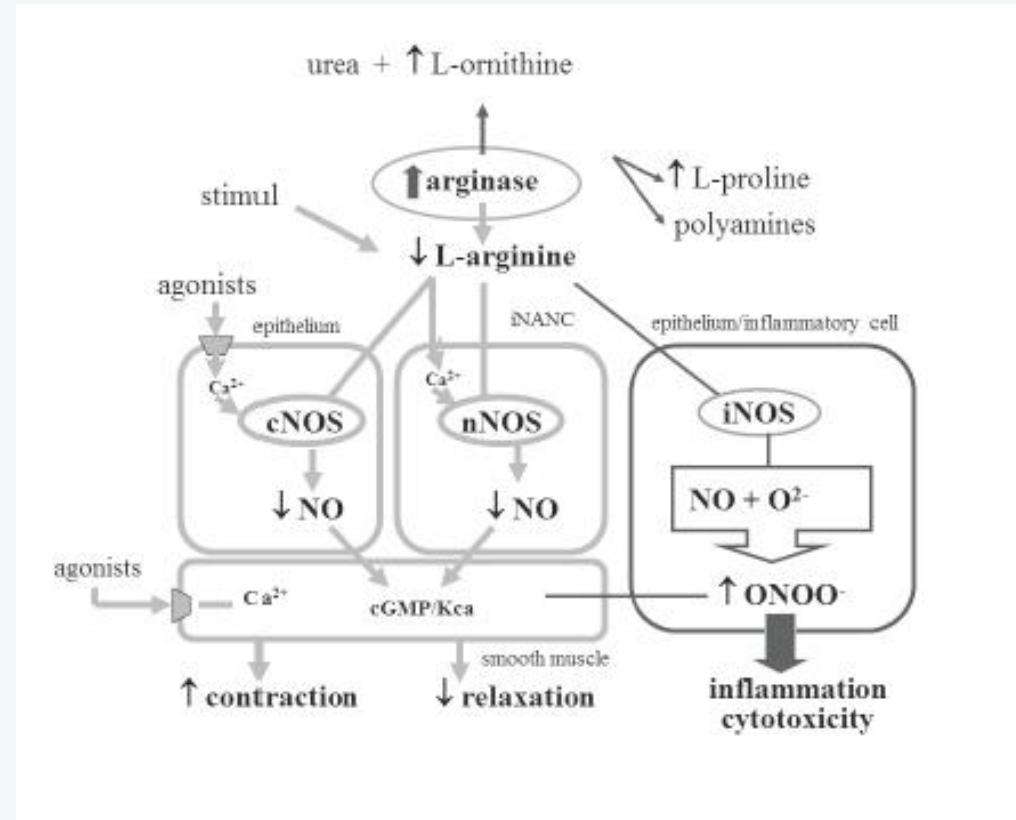
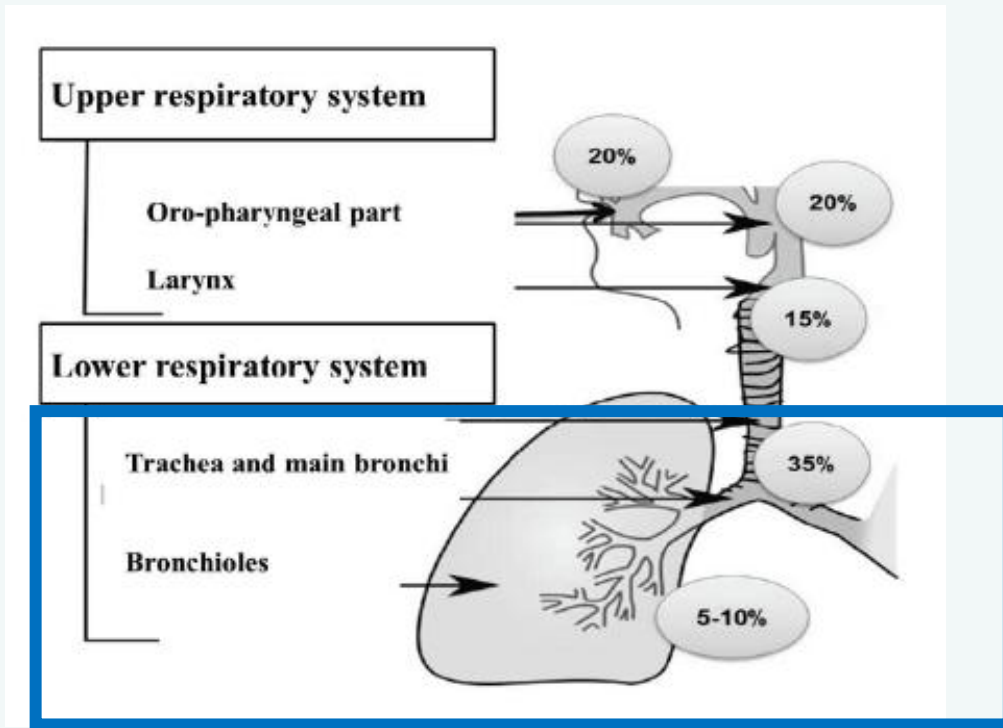
Lee JH, et al. *J Thorac Dis* 2023;15:5844-55.

Sadeghi MH, et al. *Ann Allergy Asthma Immunol* 2018;120:285-91

Rybka-Frączek A, et al *ERJ Open Res* 2021;7:00432-2021

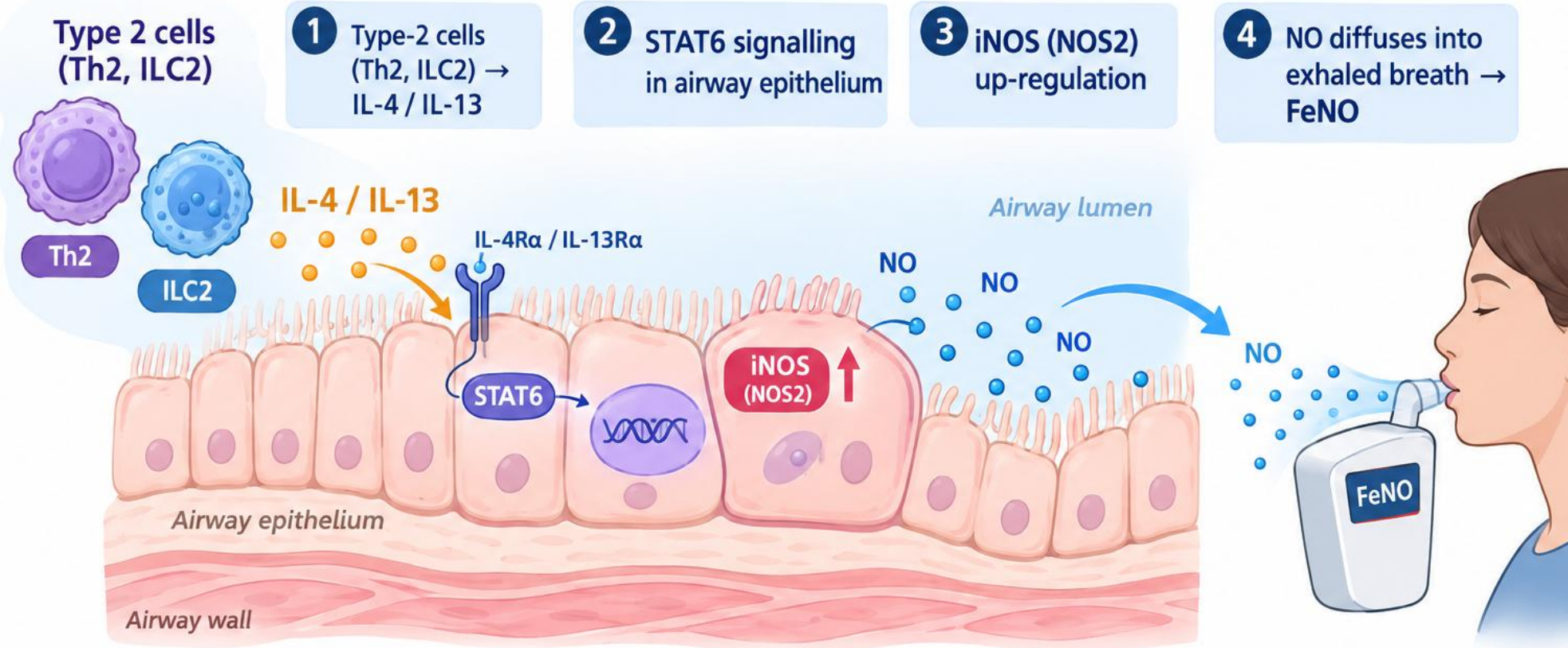
Fractional exhaled nitric oxide (FeNO)

- Point-of-care, < 2 minutes, non-invasive
- Standardized measurement at an expiratory flow of 50 mL/s
- Reproducible when measured under comparable conditions
- But a surrogate, with confounders



- **L-arginine → NO + L-citrulline**
Catalyzed by nitric oxide synthase
- **IL-4 / IL-13 → epithelial iNOS upregulation**
Major source of increased FeNO in T2 airway inflammation
- **Increased NO and oxidative stress**
Airway hyperresponsiveness, mucus secretion and impaired ciliary function
- **Sensory nerve activation**
TRPA1, TRPV1 and P2X3 pathways contribute to the cough reflex

What FeNO measures: epithelial iNOS by IL-4/ IL-13



Factors influencing FeNO

↑ Raises FeNO

- Atopy, ongoing allergen exposure, allergic rhinitis
- Respiratory tract infection (viral URI — up to weeks)
- Nitrate-rich food (spinach, lettuce, celery) on the test day
- Bronchodilator within 1 h
- Male sex, greater height, older age (adults)
- Other eosinophilic disease: EGPA, eosinophilic pneumonia, COPD with T2 phenotype

↓ Lowers FeNO

- Current smoking — acutely and chronically (recovers after cessation)
- ICS, OCS, LTRA — fall evident within 2 days; may mask T2 cough
- Spirometry or bronchoprovocation within 1 h (~10% drop), bronchoconstriction, vigorous exercise
- Coffee, water, food within 1 h
- Pulmonary hypertension, cystic fibrosis, PCD (very low nasal NO)
- Obesity (modest effect)

- FeNO first, spirometry after
- Ask about smoking, ICS/LTRA, recent URI
- No food, coffee or smoking for 1 h
- Same analyser for follow-up (electrochemical devices read 4–10 ppb lower than chemiluminescence)

Interpretation of FeNO: ATS clinical practice guideline (2011)

- Cut points rather than reference values are suggested, because healthy and asthmatic populations overlap widely
- Measured at an exhalation flow of 50 mL/s; different cut points apply to children under 12 years

	Low	Intermediate	High
FeNO, adults	< 25 ppb	25 – 50 ppb	> 50 ppb
Eosinophilic airway inflammation	Unlikely	Interpret cautiously with reference to the clinical context	Likely
Responsiveness to corticosteroids	Unlikely	Uncertain	Likely in symptomatic patients
Strength of recommendation	Strong, moderate quality	Strong, low quality	Strong, moderate quality

- Chronic cough guidelines (ERS 2020, BTS 2023) adopt only the lower cut point: FeNO > 25 ppb supports a trial of ICS

The landmark trial (2005)

- Use of exhaled nitric oxide measurements to guide treatment in chronic asthma
- Single-center, (Dunedin, NZ), single-blind RCT
- 97 adults on regular ICS
 - Phase 1 dose optimization, then 12-month follow-up (phase 2)
- FeNO-guided (cut-off 15 ppb at 250 mL/s $\approx$ 35 ppb at 50 mL/s) vs. guideline-based algorithm
- **Primary outcome:** exacerbation frequency
- **Secondary outcome:** mean daily fluticasone dose

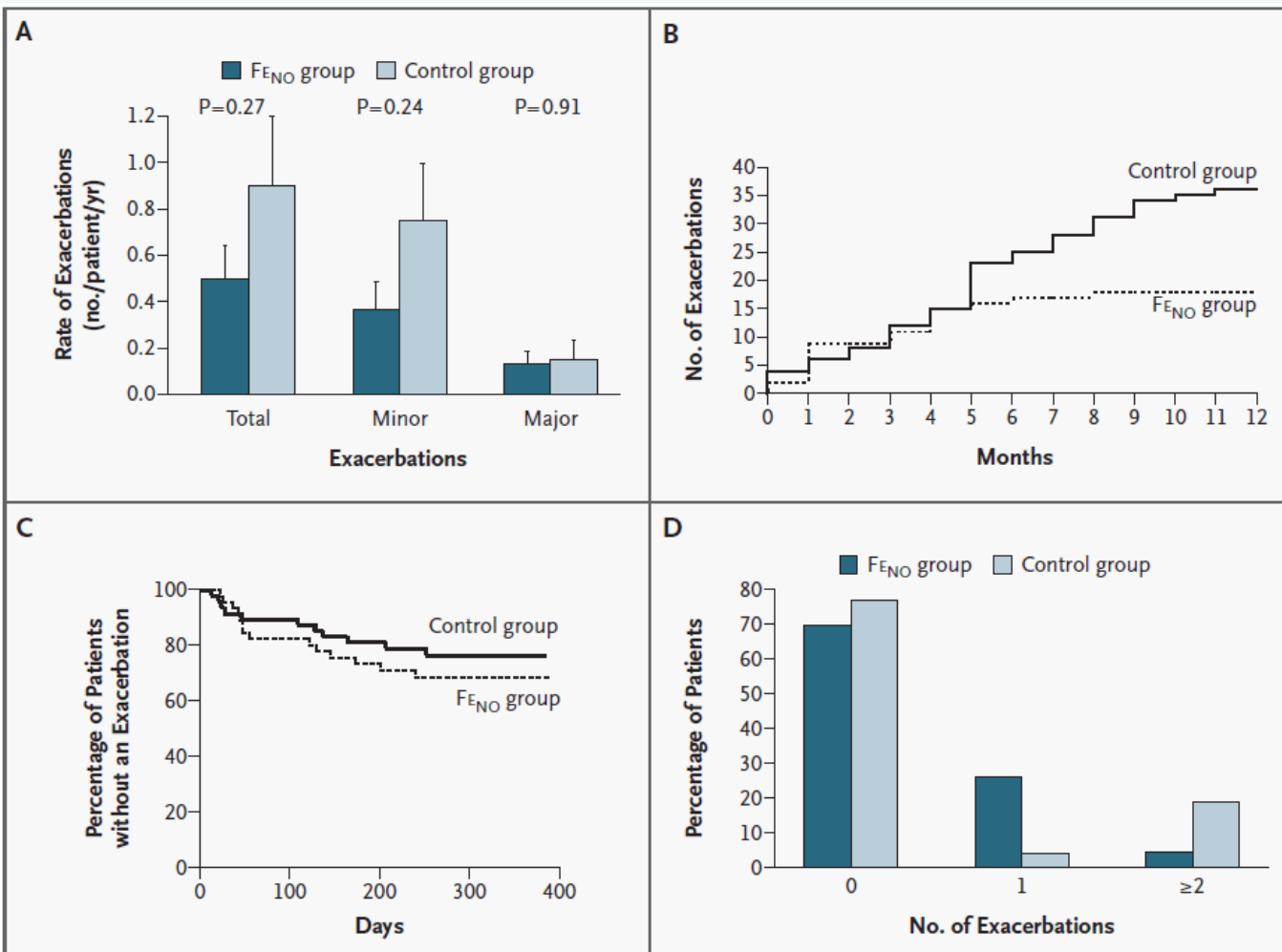


Figure 2. Rates of Exacerbation.

Panel A shows the mean rates of total exacerbations of asthma and of minor and major exacerbations during phase 2. Error bars represent SEs. In Panel B, the cumulative number of exacerbations of asthma during phase 2 is shown; $P=0.27$ for the comparison between groups. Panel C shows the results of a Kaplan–Meier analysis of the time to a first exacerbation of asthma in each group during phase 2. There was no significant difference between the two groups ($P=0.39$). Panel D shows the frequency distribution of patients who had zero, one, and two or more exacerbations during phase 2.

- **0.49** episode per patient per year in the FeNO group (95% CI, 0.20 to 0.78) and **0.90** in the control group (95% CI, 0.31 to 1.49)
- Nonsignificant reduction of **45.6%** (95% CI, 78.6 to 54.5%) in the FeNO group.

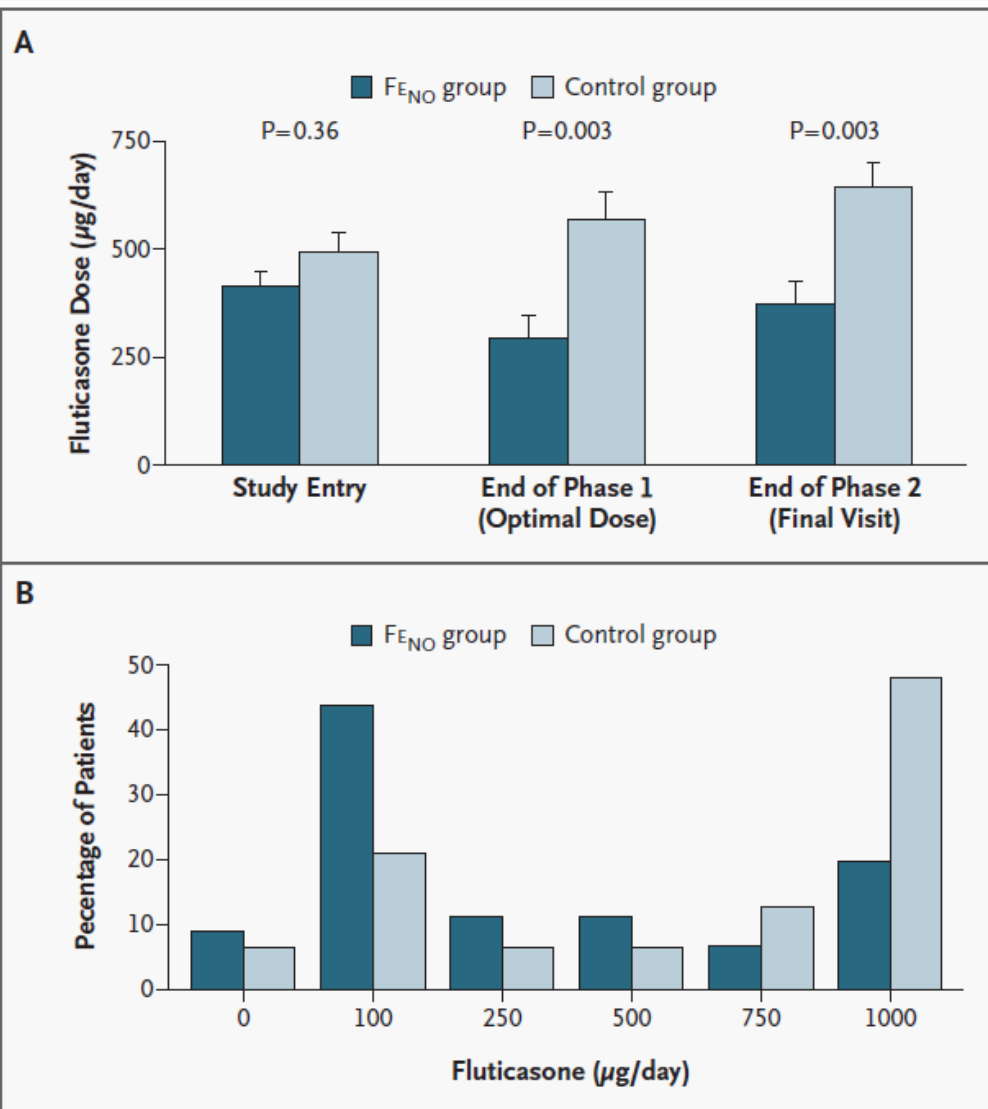


Figure 3. Doses of Inhaled Fluticasone.

Panel A shows the mean dose of inhaled fluticasone at study entry, the optimal dose, and the dose at the final visit. Error bars represent SDs. Panel B shows the distribution of doses of inhaled fluticasone at the end of the study. P=0.008 for the comparison between the two groups.

- The mean dose of inhaled corticosteroid were **370 µg per day** for the FeNO group (95% CI, 263 to 477) and **641 µg per day** for the control group (95% CI, 526 to 756; P=0.003)
- Difference of **270 µg per day** (95% CI, 112 to 430; P = 0.003)

- Less steroid, equal control: clear. Fewer exacerbations: a trend in 97 patients.
- The next decade asked whether the trend was real.

Diagnostic utility of FeNO

- Higher FeNO in asthma and eosinophilic bronchitis
- Useful for identifying eosinophilic/Type 2 inflammation in chronic cough
- Key strength: high specificity

Study	Asthma/CVA	Rhinitis/UACS	GERD	Non-asthmatic cough	Healthy controls
Young adults 18–45 with chronic cough	86 ppb	37 ppb	14.8 ppb	—	13 ppb
Cough ≥ 3 weeks	75.0 ppb	—	—	16.7 ppb	28.3 ppb

Lee JH et al. J Thorac Dis 2023;15:5844-57
Kowal K et al. J Asthma 2009;46:692-8
Chatkin JM et al. Am J Respir Crit Care Med 1999;159:1810-3

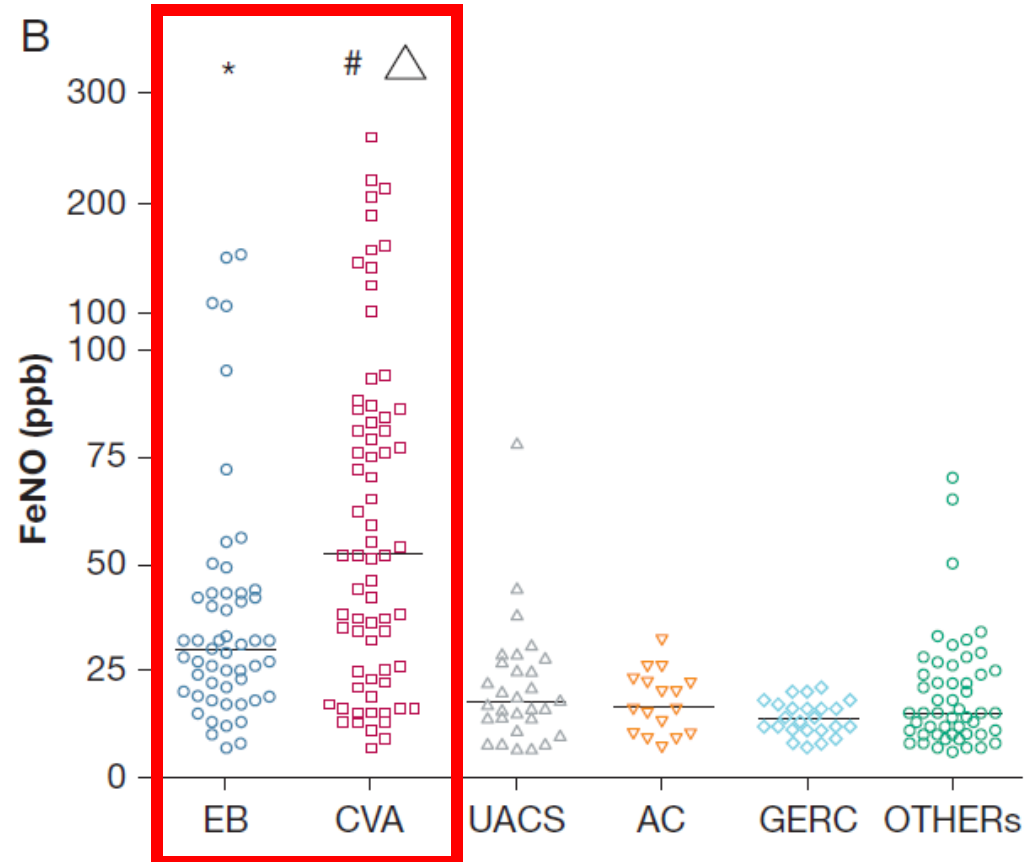


Figure 2 – Exhaled NO values by diagnostic category. A, FeNO value in CRC ($n = 139$) was significantly higher than that in NCRC ($n = 105$) ($P < .01$). B, FeNO values by diagnostic category. FeNO values in CVA and EB were significantly higher than those in AC, UACS, GERC, others, and the healthy control subjects (* $P < .01$ and # $P < .01$ respectively). FeNO values in CVA were significantly higher than those in EB ($\Delta P < .01$). See the [Figure 1](#) legend for expansion of abbreviations.

- **CVA:** 52.0 ppb (24.0-85.0)
- **EB:** 30.0 ppb (19.5-43.0)
- **AC:** 16.0 ppb (10.0-22.5)
- **UACS:** 17.5 ppb (13.3-27.3)
- **GERD:** 13.5 ppb (11.0-16.8)
- **Others:** 15.0 ppb (10.0-25.0)
- **Healthy:** 18.0 ppb (13.0-27.0)

Diagnostic utility of FeNO

- Diagnostic accuracy of FeNO in a meta analysis
- Diagnostic precision of FeNO may be considered moderate

Study	Sensitivity (95% CI)	Specificity (95% CI)	AUC (95% CI)
Cough-variant asthma	0.72 (0.61–0.81)	0.85 (0.81–0.88)	0.87 (0.83–0.89)
CVA or eosinophilic bronchitis	0.72 (0.61–0.81)	0.85 (0.81–0.88)	0.89 (0.86–0.92)

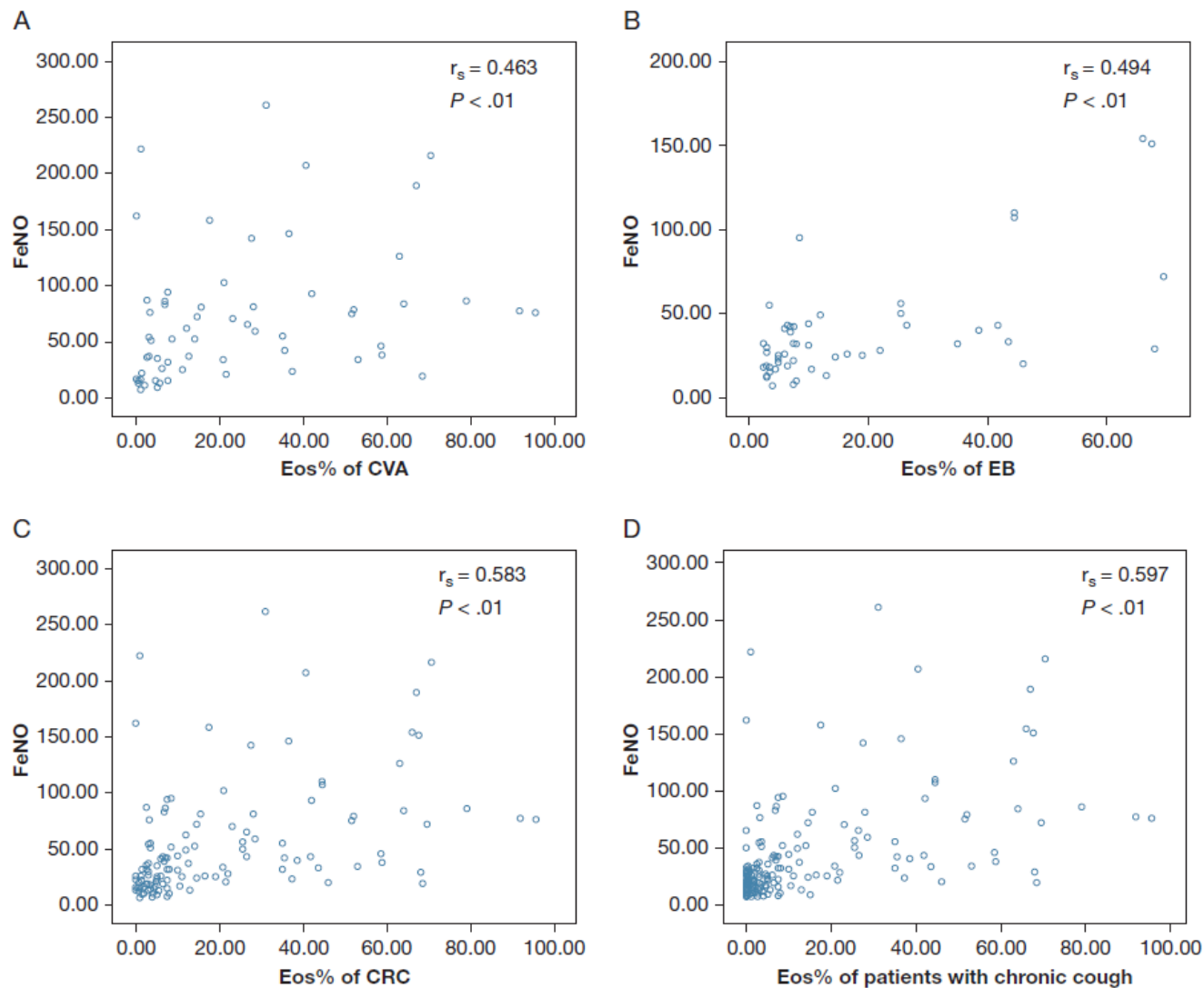
FeNO & Sputum eosinophils

- Sputum eosinophilia is usually accompanied by high FeNO
- Correlation coefficient between sputum eosinophils (%) and FeNO in chronic cough range from 0.57 to 0.666
- 1/3 patients with sputum eosinophilia (> 2.5%) had FeNO below 31.5ppb
- Diagnostic precision of FeNO May be considered moderate
- Different drivers: IL-5 → eosinophils, IL-13 → FeNO

Lee JH et al. J Thorac Dis 2023;15:5844-57

Song WJ et al. J Allergy Clin Immunol 2017;140:701-9

Zhang L et al. J Asthma 2020;57:335-42

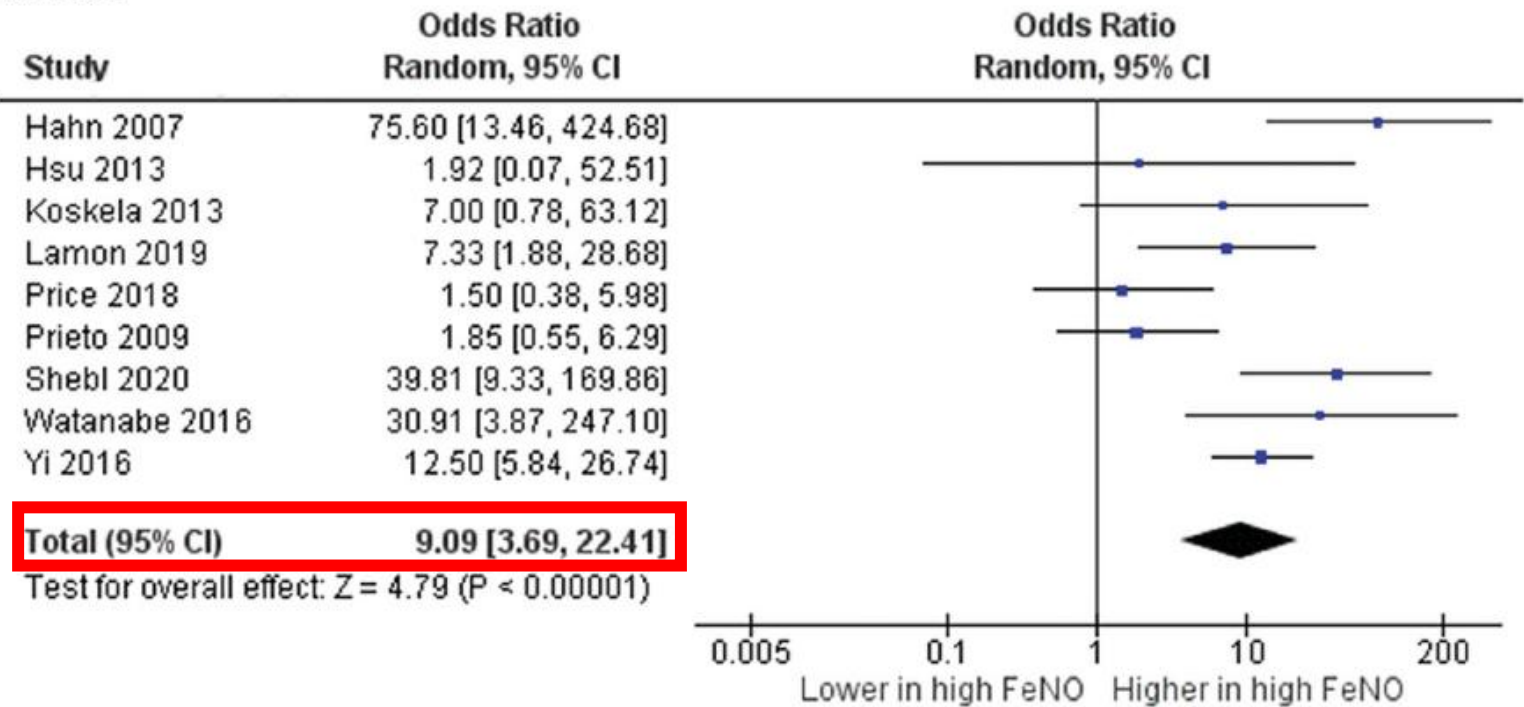


- FeNO shows a moderate correlation with sputum eosinophilia
- The association is consistent across subgroups, but not strong
- FeNO reflects eosinophilic airway inflammation, but cannot replace sputum eosinophils

Figure 4 – Correlation of FeNO and percentage of sputum eosinophils (Eos%) in patients with CVA, EB, CRC, and all patients with chronic cough. A, Correlation between FeNO and Eos% was found in 63 patients with CVA ($r = 0.463$, $P < .01$). B, Correlation between FeNO and Eos% was found in 53 patients with EB ($r = 0.494$, $P < .01$). C, Correlation between FeNO and Eos% was found in 132 patients with CRC ($r = 0.583$, $P < .01$). D, Correlation between FeNO and Eos% was found in 215 patients with chronic cough ($r = 0.597$, $P < .01$). See the [Figure 1](#) legend for expansion of abbreviations.

High FeNO predicts ICS response

Panel A



Meta-analysis of 9 studies (n=740)

- 87.4% (95%CI:83.8–91.0) in 317 chronic-cough patients with a high FeNO
- 46.3% (95%CI: 41.6–51.0) in 423 low-FENO
- Corresponding OR of 9.1 (95%CI: 3.7–22.4, $p<.001$)

FeNO in predicting ICS response

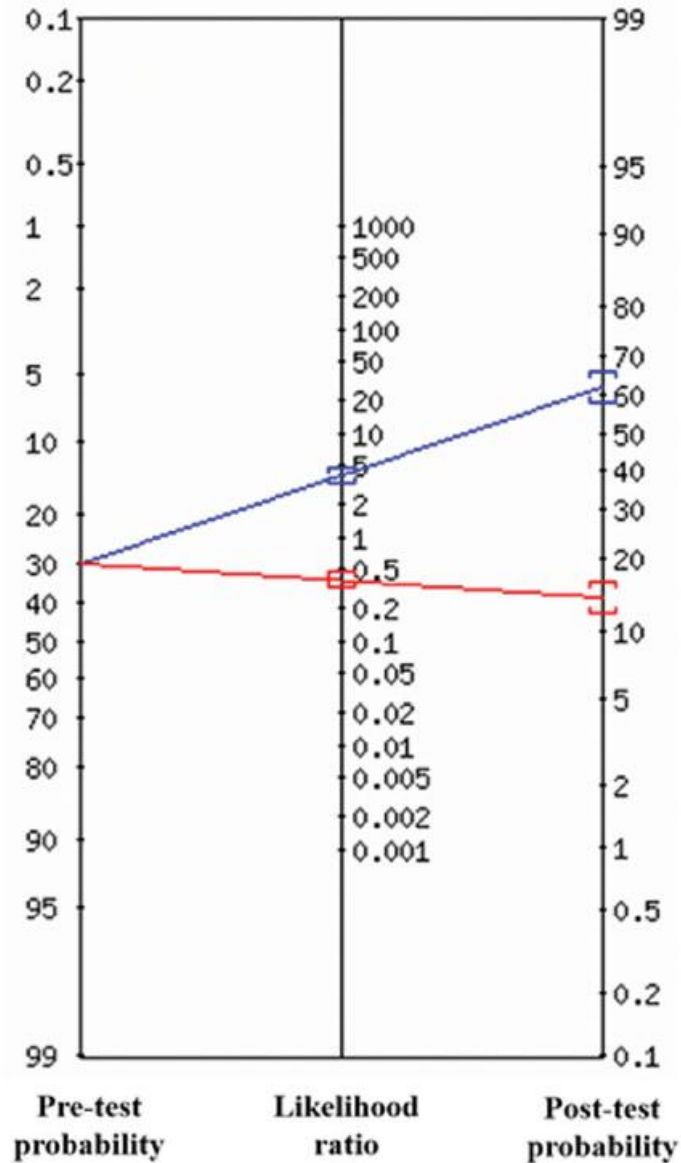
Table 3. Pooled diagnostic indexes for the association between high fractional exhaled nitric oxide (FeNO) and response to inhaled corticosteroids in sensitivity and subgroup analyses.

	SENSITIVITY ANALYSES				SUBGROUP ANALYSES	
	Exclusion of retrospective studies	Exclusion of data on smokers	Exclusion of studies not using the recommended ≥ 8-week limit for chronic cough definition	Exclusion of studies with high risk of bias and/or applicability concerns in patient selection	FeNO cut-off ≤ 25 ppb	FeNO cut-off > 25 ppb
Sensitivity (%)	54.3 (95%CI: 37.3–70.5)	64.2 (95%CI: 58.2–69.9)	76.0 (95%CI: 52.2–90.1)	79.2 (95%CI: 53.0–92.8)	49.6 (95%CI: 39.0–60.2)	77.4 (95%CI: 46.5–93.1)
Specificity (%)	83.6 (95%CI: 70.7–91.5)	83.4 (95%CI: 77.0–88.7)	78.1 (95%CI: 53.8–91.6)	73.9 (95%CI: 43.6–91.2)	79.7 (95%CI: 60.2–91.1)	81.3 (95%CI: 50.2–94.9)
PLR	3.31 (95%CI: 1.51–7.28)	2.55 (95%CI: 0.83–7.80)	3.47 (95%CI: 1.65–7.30)	3.04 (95%CI: 1.31–7.05)	2.44 (95%CI: 1.12–5.33)	4.14 (95%CI: 1.50–11.41)
NLR	0.55 (95%CI: 0.35–0.84)	0.36 (95%CI: 0.20–0.67)	0.31 (95%CI: 0.16–0.61)	0.28 (95%CI: 0.12–0.64)	0.63 (95%CI: 0.48–0.84)	0.28 (95%CI: 0.11–0.69)
HSROC _{AUC}	0.77 (95%CI: 0.53–0.91)	0.78 (95%CI: 0.54–0.91)	0.83 (95%CI: 0.55–0.90)	0.82 (95%CI: 0.64–0.89)	0.52 (95%CI: 0.47–0.63)	0.83 (95%CI: 0.62–0.94)

PLR: positive likelihood ratio; NLR: negative likelihood ratio; SROC_{AUC}: area under the summary receiver operating characteristic curve; Q* index: intercept of the summary receiver operating characteristic curve; HSROC_{AUC}: area under the hierarchical summary receiver operating characteristic curve.

- FeNO ≤25 ppb: poor prediction of ICS response (OR 3.9; AUC 0.52)
- FeNO >25 ppb: substantially better predictive performance (OR 13.5; AUC 0.83)
- Pooled estimates : sensitivity 68.5%, specificity 81.9%
- Responders had FeNO 23 ppb higher than non-responders

Fagan's nomogram



— Change in probability if positive test

— Change in probability if negative test

- High FeNO raises the chance of ICS response to 62% (pre-test probability 30%)
- Low FeNO → 14%: does not rule out ICS response

ERS guidelines on the diagnosis and treatment of chronic cough (2020)

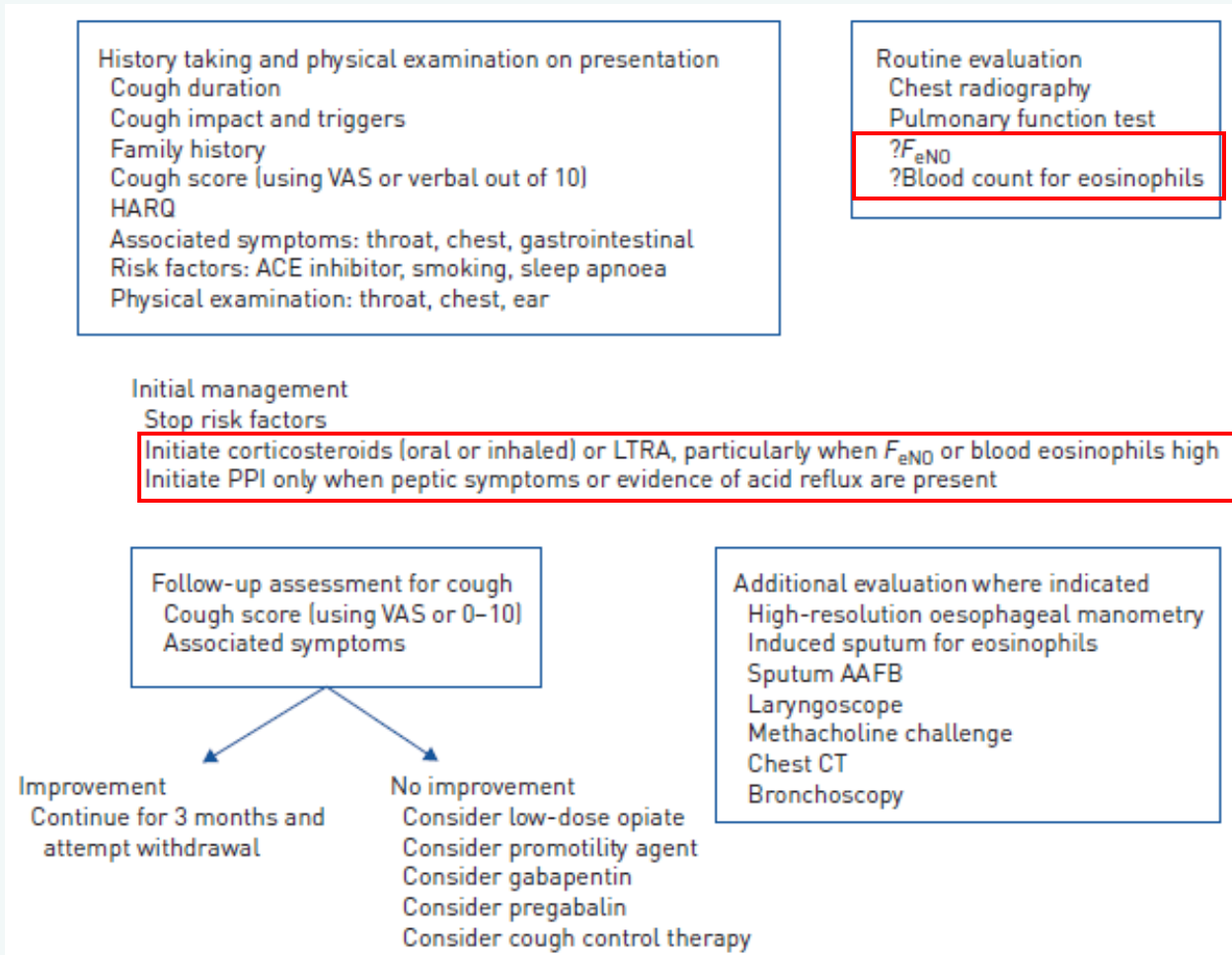
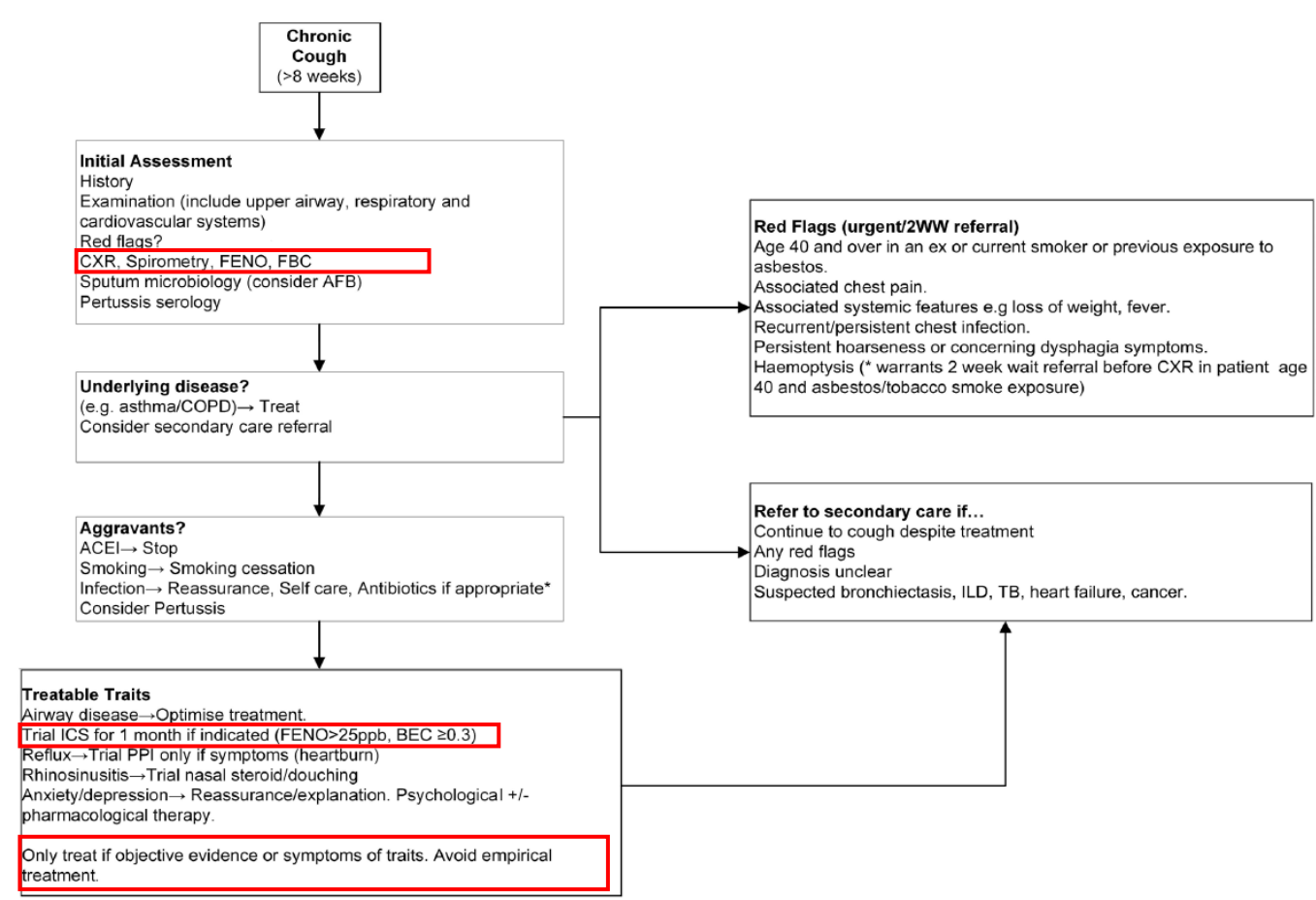
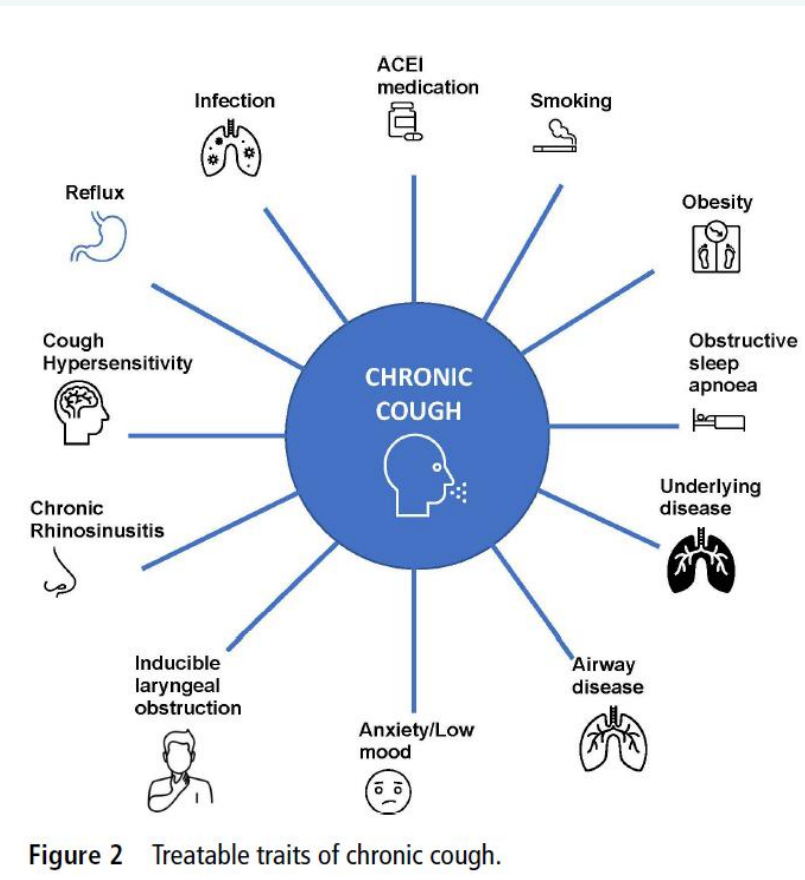


FIGURE 1 Cough assessment in adults. VAS: visual analogue scale; HARQ: Hull Airway Reflux Questionnaire; ACE: angiotensin-converting enzyme; F_{eNO} : exhaled nitric oxide fraction; LTRA: leukotriene receptor antagonist; PPI: proton-pump inhibitor; AAFB: alcohol and acid-fast bacilli; CT: computed tomography.

- Asthma, reflux, and rhinitis reframed as **treatable traits**
- **FeNO** and **blood eosinophils** introduced into routine assessment (limited evidence / research recommendation)
- **Trial of ICS or LTRA for 2–4 weeks**, especially when FeNO or blood eosinophils are elevated
- **Empirical PPI no longer routinely recommended**
- Neuromodulators formally incorporated for refractory chronic cough

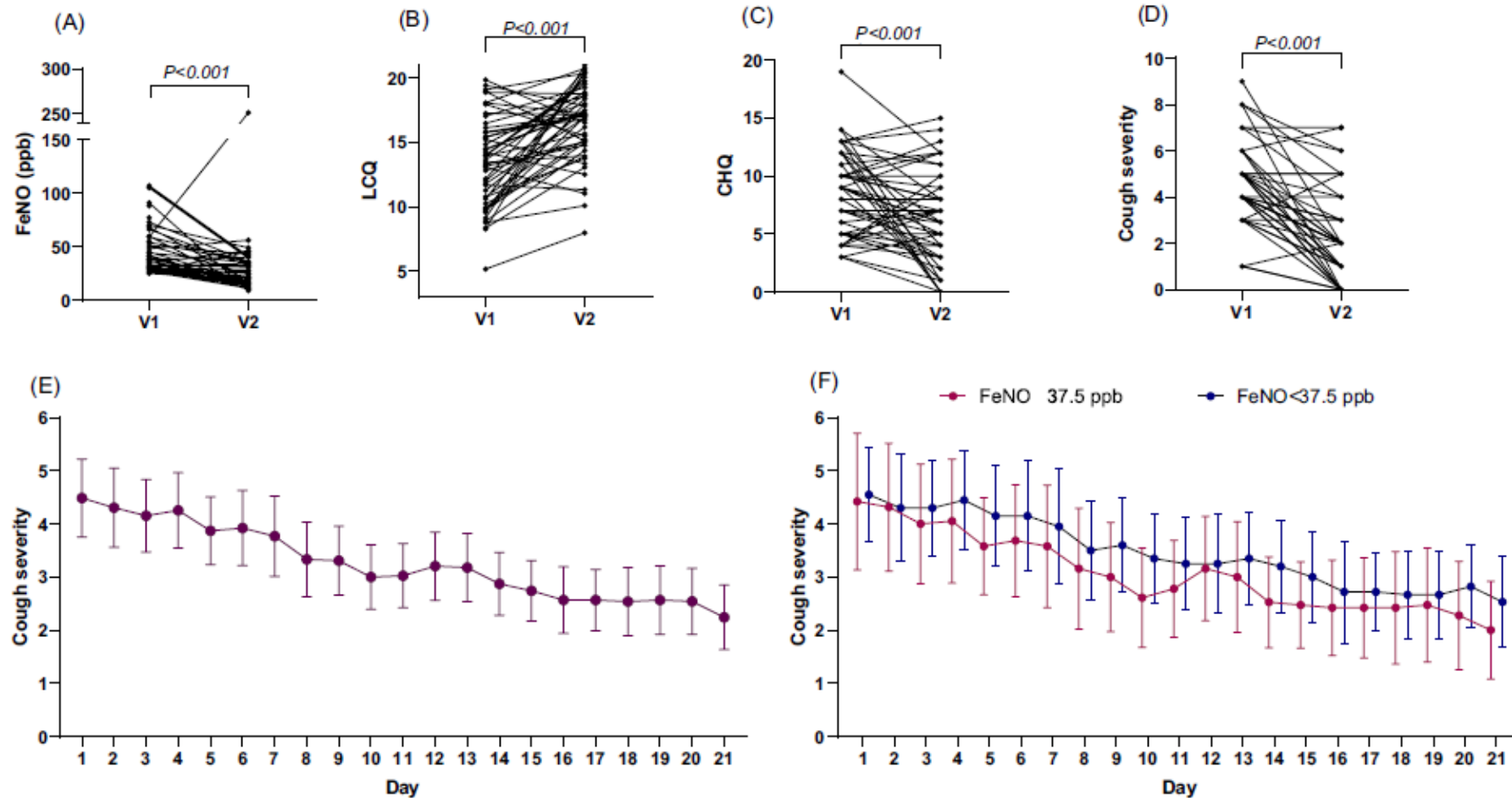
BTS Clinical Statement on Chronic cough in adults (2023)

- First guideline to make **FeNO** part of the basic work-up
- Only treat if objective evidence or symptoms of traits
- Avoid empirical treatment



Korean prospective single-arm study

- 50 adults with chronic cough
- FeNO $\geq$ 25 ppb, FEV₁/FVC $\geq$ 0.70,
- No other apparent cause, non-smokers
- Fluticasone furoate 200 mcg for 3 weeks (multi-center, no placebo arm)

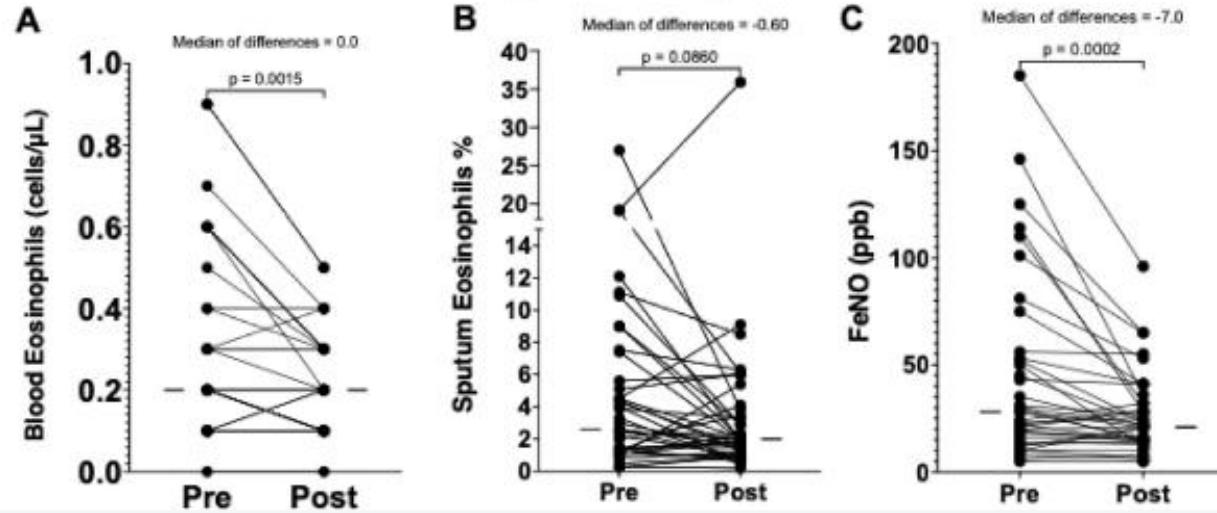


- FeNO fell from 37.5 to 22.0 ppb; LCQ, CHQ and cough severity all improved
- Daily cough severity improved slowly and steadily over 21 days
- No correlation between FeNO and cough — neither at baseline ($r = 0.06$) nor between change in FeNO and change in LCQ ($r = -0.28$)

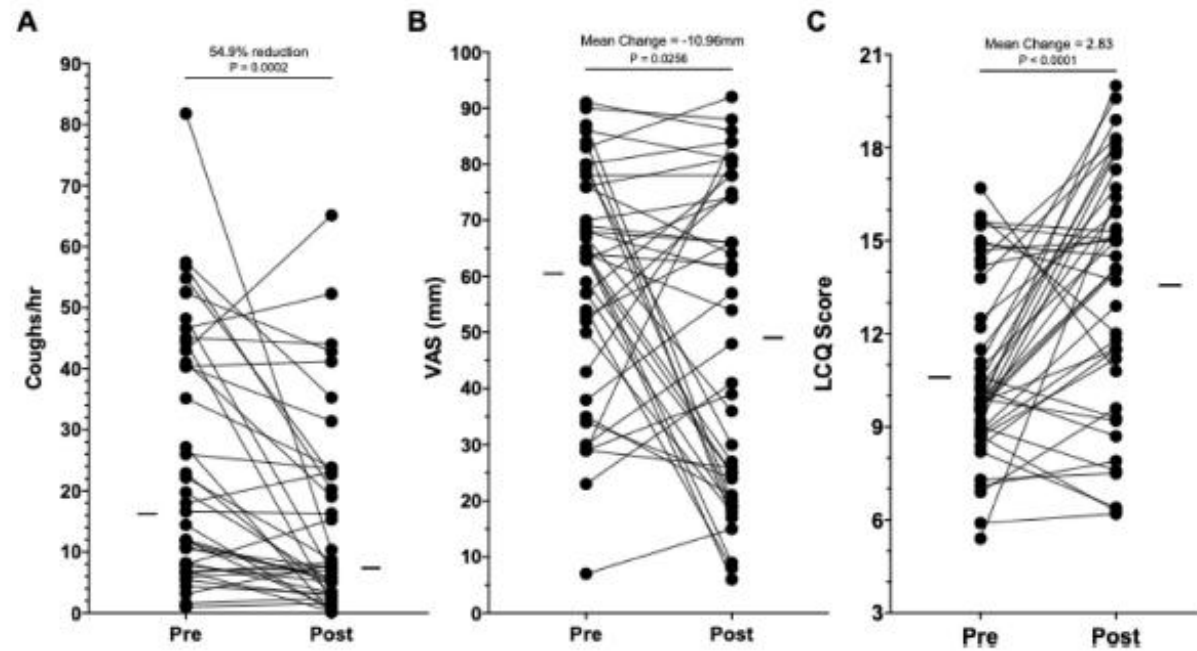
PROCOUGH Study (2026)

- Prospective single-center cohort (McMaster, Canada)
- 100 patients with chronic cough, objective 24-h cough monitoring
- **CC_{ast/EB}**: Asthma/NAEB (**n = 45**) → ICS/LABA
- **RCC**: Refractory chronic cough (**n = 55**) → neuromodulators
- Baseline FeNO **28 vs 15 ppb**
- Sputum eosinophils **2.6 vs 1.4%**
- Blood eosinophils and total IgE did not differ between groups
- Reassessed at 6–8 weeks

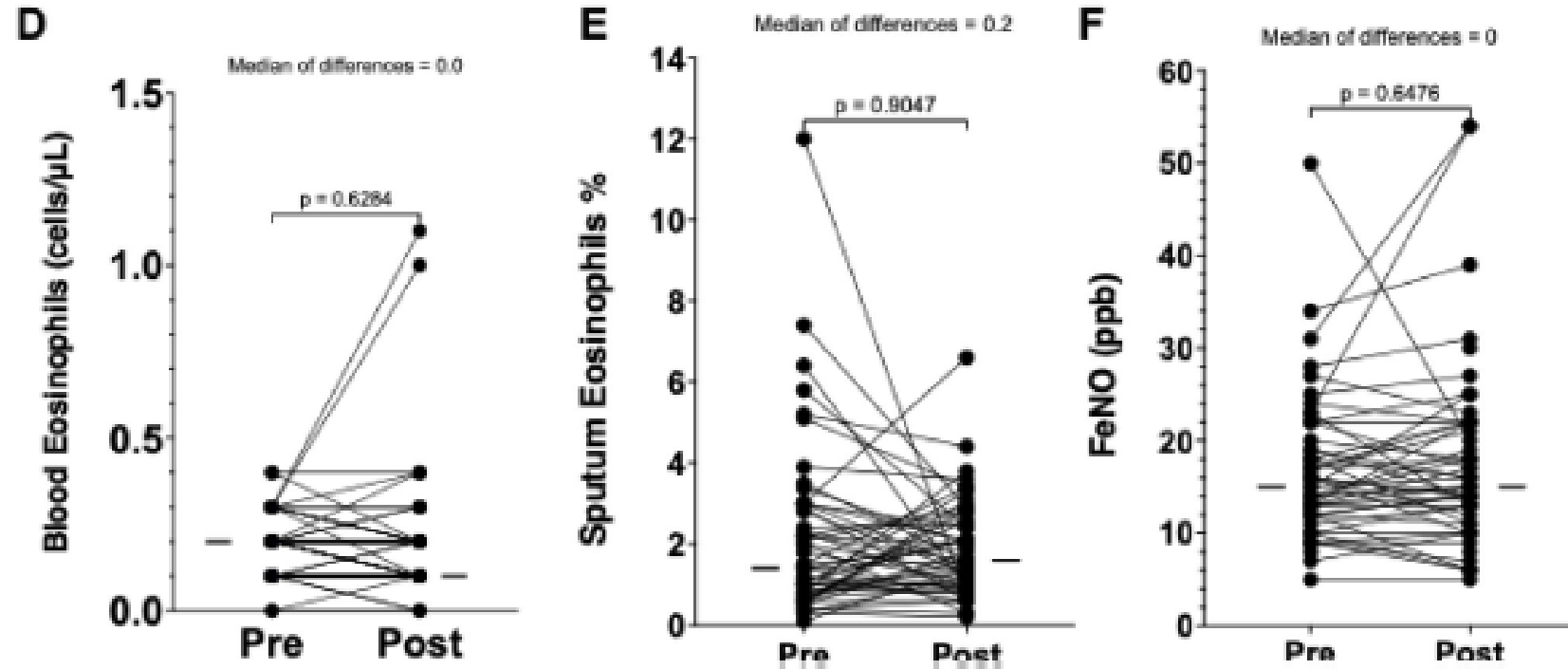
Chronic Cough secondary to Asthma/NAEB



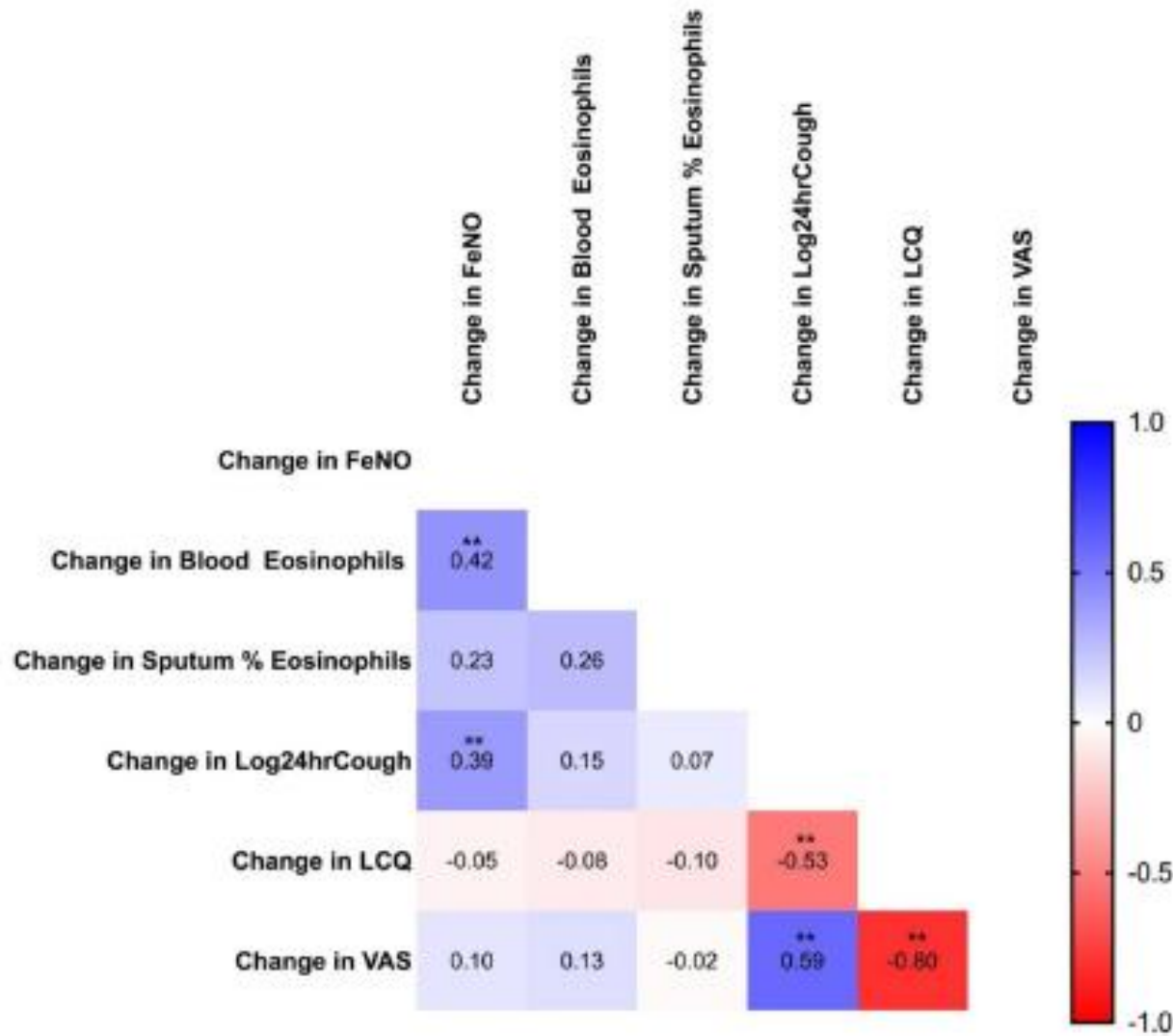
- Cough frequency -55%
- VAS -11 mm
- LCQ +2.8
- FeNO -7 ppb



Refractory Chronic Cough (RCC)



- In RCC, no biomarker changed with neuromodulator treatment



Change in FeNO correlated with change in cough frequency

Changes in blood or sputum eosinophils did not; baseline biomarkers did not reflect cough burden

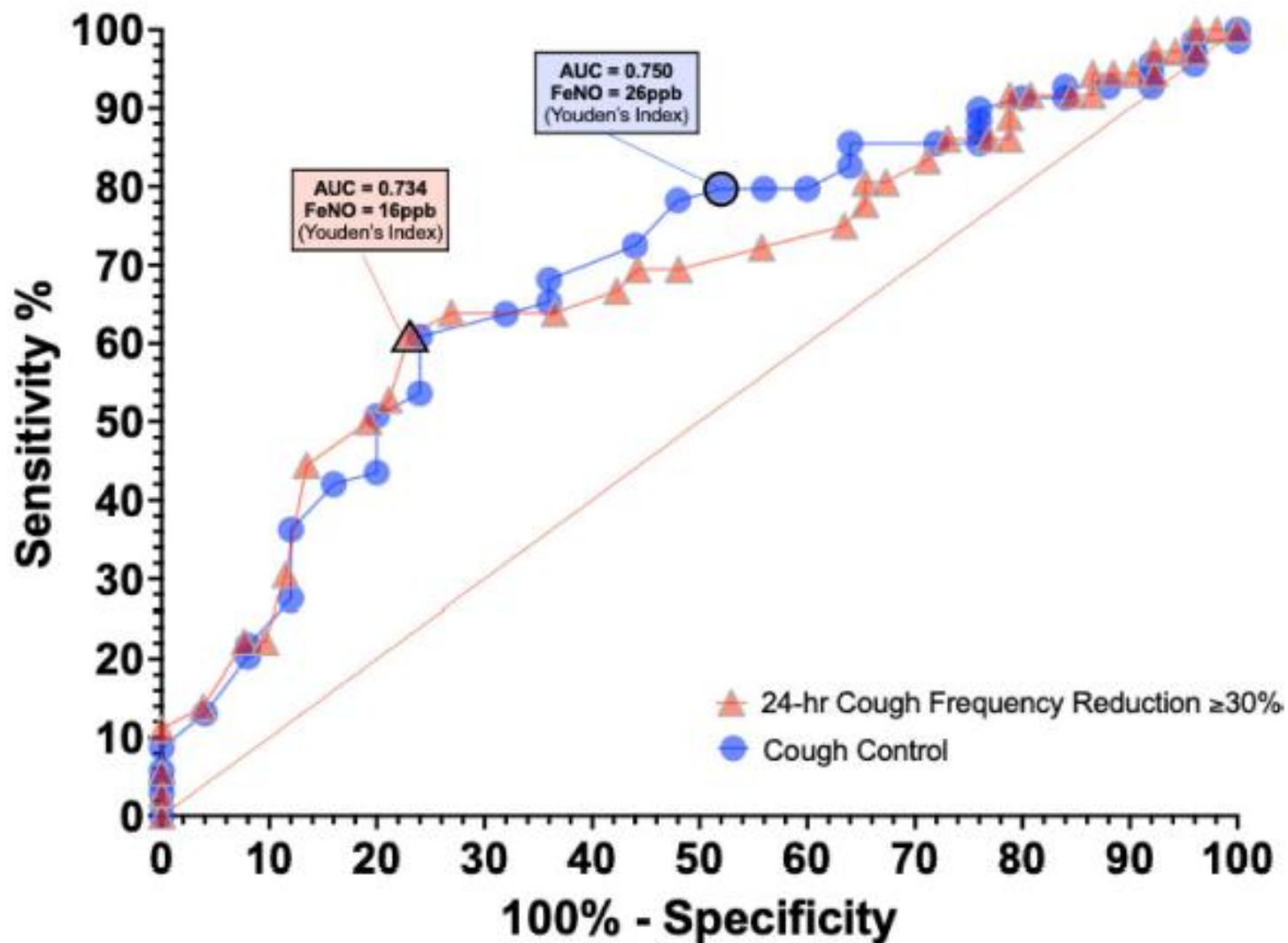


Table 2 Multivariable logistic regression: predictors of cough control

Variable	OR (Exp(E))	95% CI	p-value
Age	1.01	0.96–1.05	0.79
Sex (female)	1.15	0.37–3.60	0.81
Cough duration (years)	0.98	0.92–1.04	0.49
Total IgE (IU/L)	1.00	0.995–1.006	0.85
Blood eosinophils	0.09	0.001–7.46	0.29
FeNO (ppb)	1.03	1.00–1.05	0.048
Sputum eosinophils (%)	1.09	0.92–1.29	0.30
Log 24 h cough frequency	0.42	0.10–1.75	0.23
LCQ total score	1.08	0.84–1.39	0.54
VAS (mm)	1.00	0.96–1.04	0.84

FeNO was the only independent predictor of cough control — OR 1.03 per ppb (95% CI 1.00–1.05)

ROC: treatment response AUC 0.73 (cut-off 16 ppb) · cough control AUC 0.75 (cut-off 26 ppb, Sn 80%, Sp 44%)

Take-home message

- Start with the basic evaluation: history, chest X-ray and spirometry
- Interpret FeNO in the context of smoking, corticosteroid exposure and blood eosinophils
- FeNO reflects epithelial T2 inflammation, not a specific diagnosis or cough severity
- High FeNO supports corticosteroid-responsive cough
- Low FeNO does not exclude CVA, NAEB or ICS response
- Use FeNO to select a time-limited ICS trial, followed by objective reassessment

FeNO guides treatment; it does not determine the cause of cough

경청 해주셔서 감사합니다



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