Peripheral Eosinophils, Total IgE, and Atopy in Newly Identified Patients with Gastroduodenal Eosinophilia

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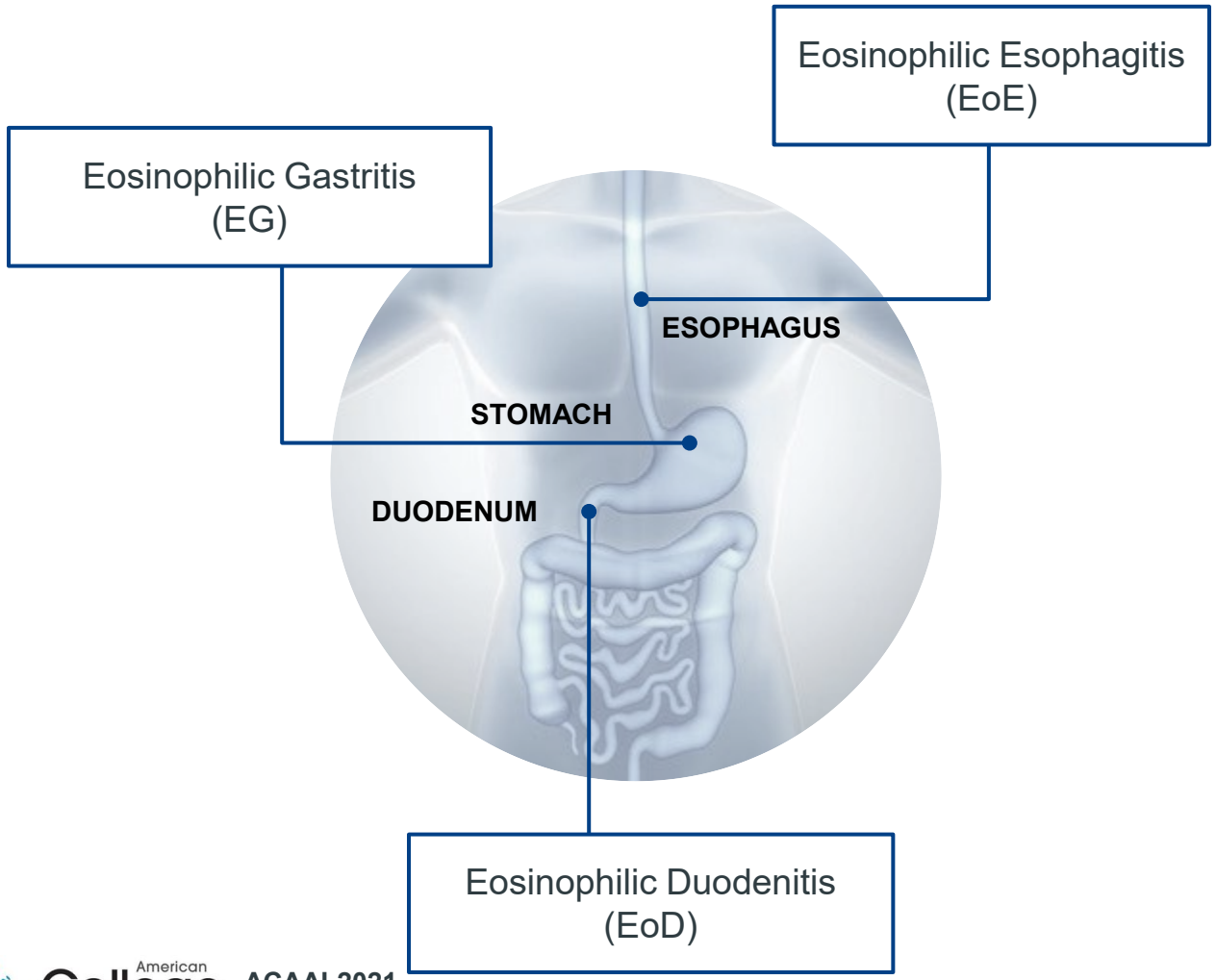
- Dr. Neal Jain is an investigator for Allakos Inc.

Background - EGIDs

- Pathologic accumulation and over-activation of eosinophils and mast cells are implicated in chronic inflammatory diseases of the gastrointestinal (GI) tract, including eosinophilic esophagitis (EoE), gastritis (EG), duodenitis (EoD), and colitis—collectively termed eosinophilic gastrointestinal diseases (EGIDs)[1,2]
- Patients with EGIDs have decreased quality of life due to chronic and often debilitating symptoms such as dysphagia, abdominal pain, bloating, nausea, vomiting, and diarrhea[3]
- Current treatment options, such as diet restriction and corticosteroids, have limited efficacy and/or are inappropriate for chronic use[4]

Sources: (1) Caldwell JM, et al. JACI 2014. (2) Youngblood BA, et al. Gastroenterology. 2019.
(3) Chehade M, er al. JACI in Practice. 2020 (4) Dellon et al, NEJM 2020.

Eosinophilic Gastrointestinal Diseases (EGIDs)



EG, EoD, EoE

Chronic Eosinophilic Inflammation of the Stomach, Duodenum, or Esophagus

- Eosinophils and mast cells are important drivers of disease
- Symptoms: abdominal pain, nausea, early satiety, loss of appetite, bloating, abdominal cramping, vomiting, diarrhea, and dysphagia (specific to EoE)
- No FDA approved treatment for EG, EoD, or EoE
- Current standard of care: diet and/or steroids

Source: Egan M, Furuta GT. Ann Allergy Asthma Immunol 121(2018) 162-167; Gonsalves M. Clin Rev. Allergy Immunol. 2019.

Background – EG/EoD Prevalence

- EG and/or EoD are thought to affect 45,000–50,000 persons in the US; this could be an underestimate[1]
  - Emerging evidence suggest these conditions are highly underdiagnosed[2]
- EG and/or EoD have been described as rare conditions found in atopic individuals with increased peripheral eosinophils and/or total IgE[3,4]
  - However, this conclusion was based on retrospective prevalence and descriptive studies or analyses of claims data, which include patients already diagnosed with EG and/or EoD

Sources: (1) Spergel JM, et al. J Ped Gastroenterology and Nutrition 2018. (2) Prussin C. Gastroenterol Clin North Am 2014
(3) Jensen ET, et al. J Ped Gastroenterology and Nutrition 2016. (4) Ingel and Hinge. World J Gastroenterol 2013.

ENIGMA: Unexpected High Discovery Rate of EG and/or EoD in Previously Undiagnosed Patients[1,2]

51 patients without history of EG and/or EoD entered ENIGMA screening

↓

51% (26/51) met symptom criteria for endoscopy and biopsy

↓

58% (15/26) EG and/or EoD[a]

- 29% (15/51) received a new diagnosis of EG and/or EoD
- Most patients without a previous diagnosis of EG and/or EoD came from general GI practices
- These patients had a history of chronic nonspecific functional GI symptoms or diagnoses

Suggests significant underdiagnosis of EG and/or EoD

Sources: (1) Dellon ES, et al. New England Journal of Medicine. 2020;383:1624-34. (2) Peterson KA et al. AJG. 2020 (ACG 2020 presentation)
a. Patients who met symptom criteria and ≥30 eos per high-power field (hpf) in 5 gastric hpfs and/or ≥30 eos/hpf in 3 duodenal hpfs

Study Objective

- Here, we conducted a prospective study to systematically evaluate symptomatic patients endoscopically to assess the prevalence of EG and/or EoD in patients with unexplained GI symptoms, and to better understand their clinical characteristics

EG and/or EoD Prevalence Study Design

- **Study Design**
  - Prospective, multi-center study to assess the prevalence of EG and/or EoD in symptomatic patients with chronic functional GI symptoms
    - at least a 6-month history of GI symptoms without identifiable cause and were unresponsive to pharmacologic or dietary interventions,

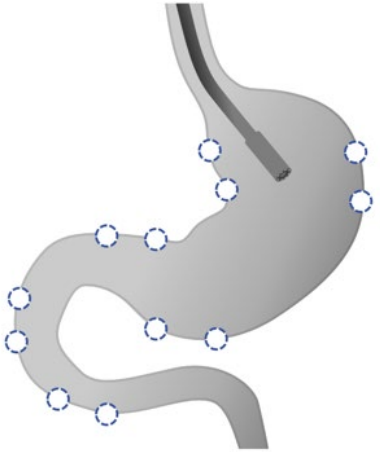
      and/or
    - a diagnosis of IBS or functional dyspepsia (FD), indicating a chronicity of symptoms
  - **A separate endoscopy study of healthy volunteers (controls) was conducted for comparison**
- **Primary Endpoint**
  - Proportion of symptomatic patients who underwent biopsy and met the histologic criteria for EG and/or EoD (≥30 eos/hpf in 5 gastric or 3 duodenal hpf)

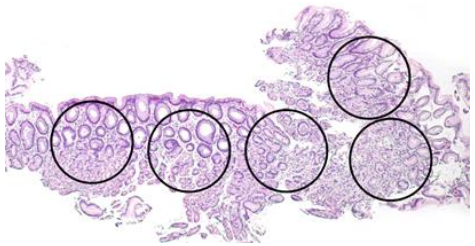
GI Symptom Questionnaire

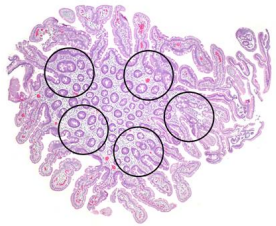
EG/EoD GI Symptom Questionnaire©

- Developed in accordance with FDA guidance on PRO development
- Captures the GI symptoms of patients on a daily basis
- Measures symptoms each on a scale of 0-10 for the following:
  - Abdominal pain
  - Nausea
  - Vomiting
  - Early satiety
  - Loss of appetite
  - Abdominal cramping
  - Bloating
  - Diarrhea
- Average daily score of ≥3 (on a scale from 0-10) for any individual symptom and a Total Symptom Score (TSS) ≥10
- Same PRO used for asymptomatic healthy volunteers (controls) who had to have an average daily score ≤1 for all symptoms and no daily score ≥3 on any day for any symptom

Systematic Biopsy and Histopathologic Assessment Protocol for Patients and Controls







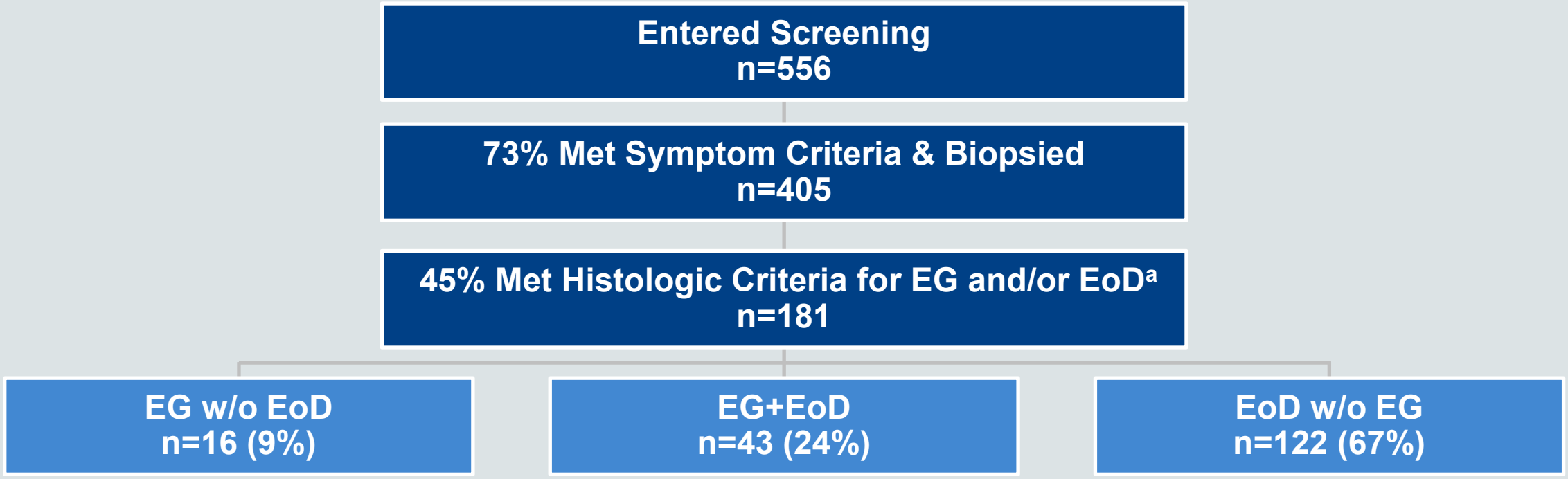
Biopsy Protocol

Stomach	• **GASTRIC ANTRUM: 4 biopsies** (2-5 cm proximal to the pylorus) • **GASTRIC CORPUS: 4 biopsies** (2 from the proximal lesser curvature and 2 from the greater curvature)
Duodenum	• **4 biopsies** from the duodenum, 2 each from the descending and horizontal parts

Assessment Protocol

- Biopsy samples were collected and sent to the central lab for fixing and staining and then evaluated by an external expert pathologist, who was blinded to all patient demographic, clinical, and endoscopic data
- Eosinophils and mast cells were counted systematically in a minimum of 5 non-overlapping hpfs in at least 12 biopsies to avoid missing areas of infiltration
- Gastric biopsies were graded using the Sydney System on inflammation, metaplasia, atrophy, and reactive gastropathy; the Marsh Scale Classification was used to grade duodenal samples

High Prevalence of EG and/or EoD in Patients with Chronic Unexplained GI Symptoms



33% (181/556) of patients with chronic functional GI symptoms and 45% (181/405) of patients with moderate-severe symptoms who underwent biopsy met histologic criteria for EG and/or EoD

a Patients who met symptom criteria and ≥30 eos/hpf in 5 gastric hpfs and/or ≥30 eos/hpf in 3 duodenal hpfs

Features of Patients with EG and/or EoD

Patient Characteristics		Met Histologic[a] Criteria for EG and/or EoD n=181
Mean age, years (range)		45 (19-78)
Female sex, %		73%
White, %		85%
Weight, median, kg		83
TSS [0-80], mean ±SD		31.3 ±11.2
History of	GI symptoms[b], mean years	11
	GERD, IBS, FD, and/or EoE, %	93%
	GERD, %	65%
	IBS, %	55%
	FD, %	15%
	Atopy[c], %	48%
	EoE, %	2%

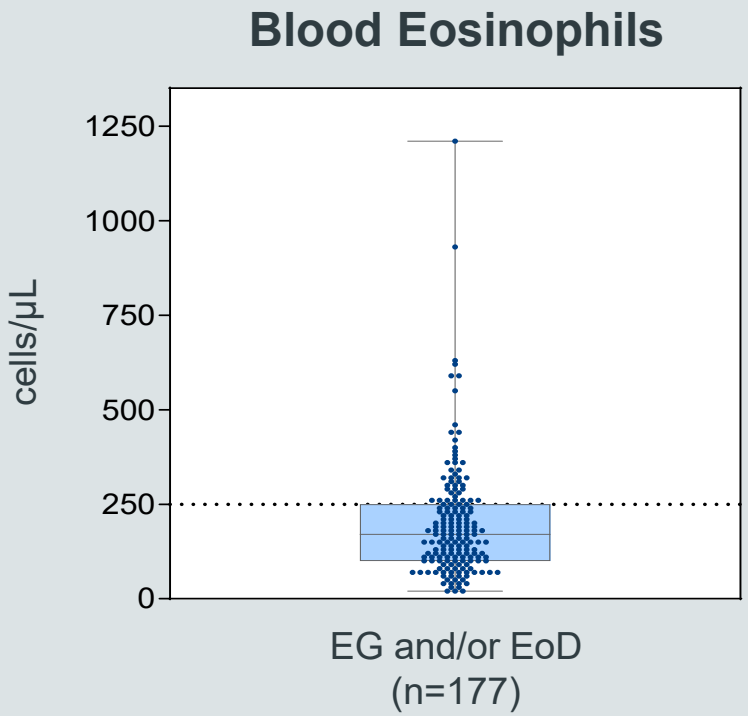
a Patients who met symptom criteria and ≥30 eos/hpf in 5 gastric hpfs and/or ≥30 eos/hpf in 3 duodenal hpfs
b Other prior GI diagnoses included other functional GI disorders, such as chronic abdominal pain or functional diarrhea
c Asthma, allergic rhinitis, atopic dermatitis and/or food allergy

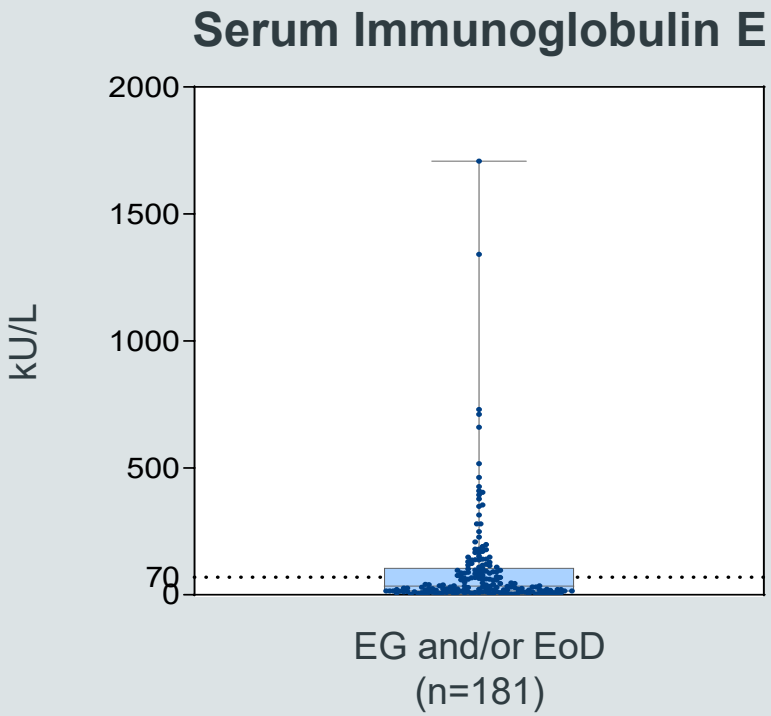
Features of Patients with EG and/or EoD

Patient Characteristics		Met Histologic[a] Criteria for EG and/or EoD n=181
Blood eosinophils	Cells/μL, median (IQR)	170 (100-250)
	Blood eos ≥500 cells/μL, %	4%
	Blood eos ≥1500 cells/μL, %	0%
Immunoglobin E	kU/L, median (IQR)	34 (14-103)

a Patients who met symptom criteria and ≥30 eos/hpf in 5 gastric hpfs and/or ≥30 eos/hpf in 3 duodenal hpfs

Blood Eosinophilia and IgE in Patients with EG and/or EoD

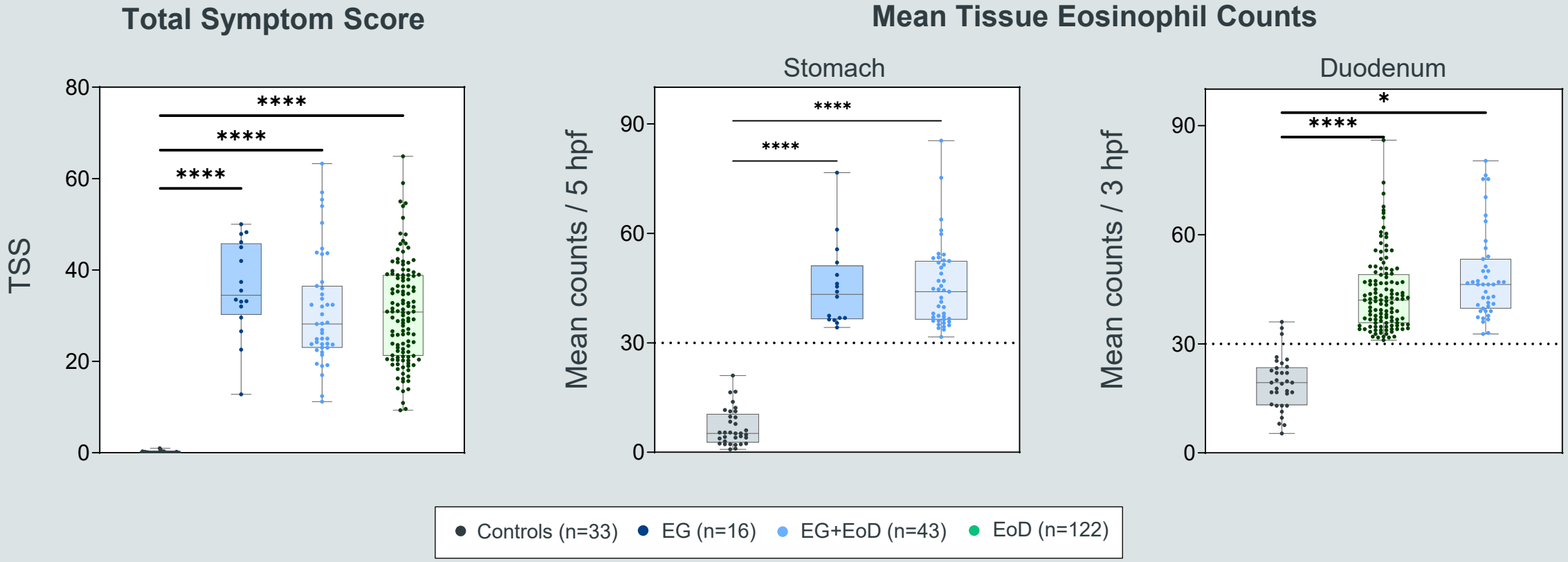




Of patients who met histologic criteria for EG and/or EoD, 27% and 4% had ≥250 eosinophils/µl and ≥500 eosinophils/µl, respectively; The median total IgE was 34 kU/L (inter-quartile range, 14–103 kU/L), and 64% of patients had IgE <70 kU/L

* P<0.05; ** P<0.01; *** P<0.0001; **** P<0.0001

Total Symptom Scores and Mean Eosinophil Counts in Patients vs. Asymptomatic Controls



45% (181/405) of patients and 6% (2/33) of asymptomatic controls met histologic criteria for EG/EoD (Odds ratio=12.52; 95% CI, 3.0–53.0; *P*<0.001)

Unpaired t-test.; * P<0.05; ** P<0.01; *** P<0.0001; **** P<0.0001

a Patients and controls used the same PRO questionnaire and underwent identical biopsy protocols. Histologic evaluation for both groups were performed by the same central pathologists

Conclusions

Endoscopy and systematic biopsy of patients with moderate–severe unexplained GI symptoms led to a high discovery rate (45%) of histologic EG and/or EoD

Most newly identified patients did not have peripheral eosinophilia or elevated IgE, indicating that EG/EoD should be considered in symptomatic patients without markers of atopy

These results suggest that there may be a spectrum or different phenotypes of EG and/or EoD, with different levels of peripheral eosinophils and IgE

Endoscopy with systematic biopsy and assessment of tissue eosinophils may lead to a precise diagnosis, including EG/EoD

We thank the patients who participated in this study, the investigators, and all study staff