

Peripheral Eosinophils and Total IgE are not Elevated in Most Newly Identified Patients With Gastroduodenal Eosinophilia

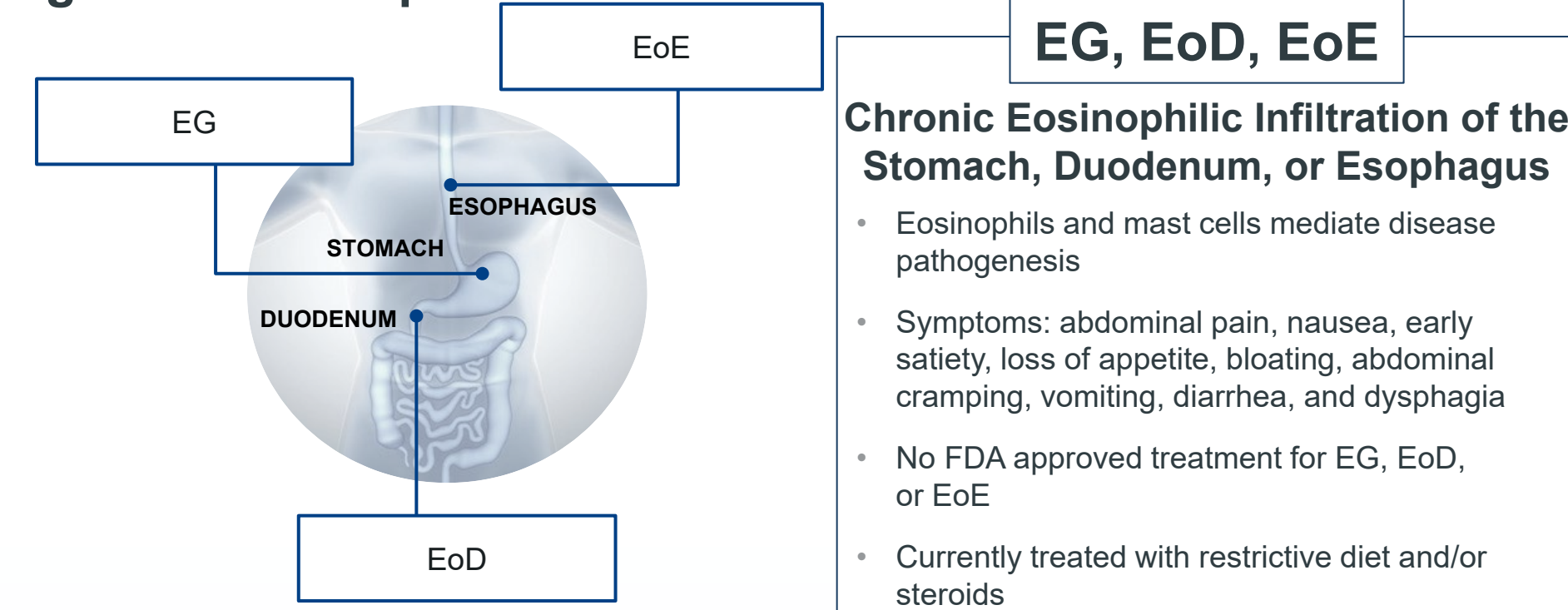
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BACKGROUND

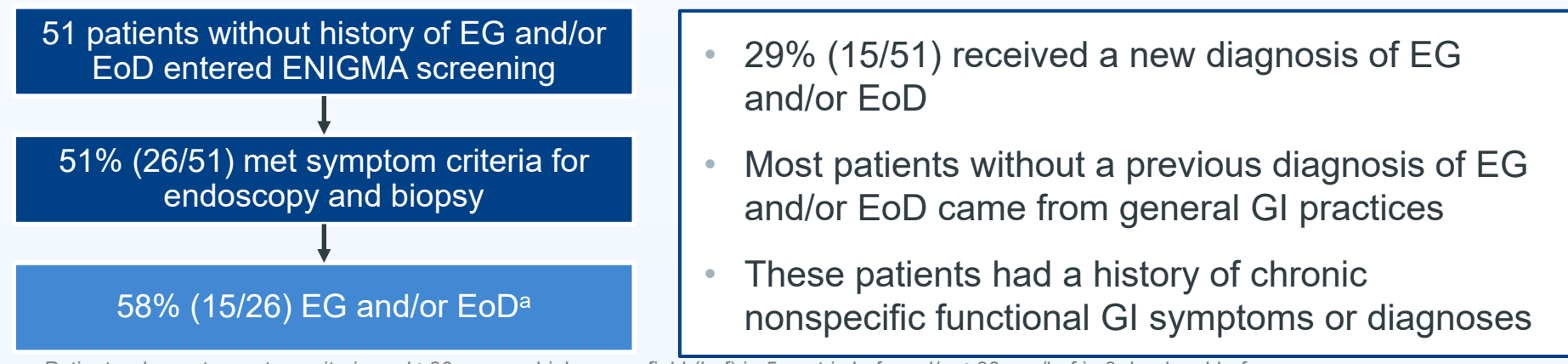
- Pathologic accumulation and over-activation of eosinophils and mast cells are implicated in chronic inflammatory diseases of the gastrointestinal (GI) tract, including eosinophilic esophagitis (EoE), gastritis (EG), duodenitis (EoD), and colitis—collectively termed eosinophilic gastrointestinal diseases (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

Figure 1. Eosinophilic GI Disorders



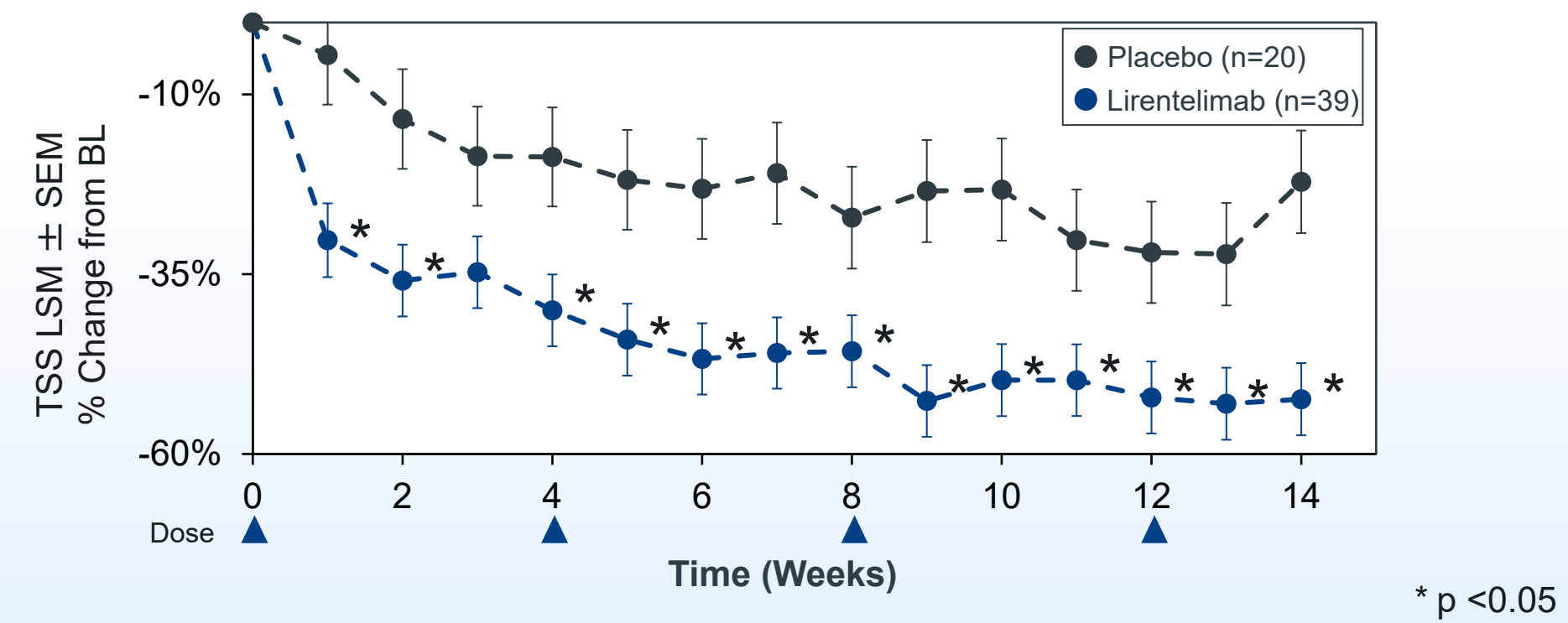
- EG and/or EoD are thought to affect 45,000–50,000 persons in the US; this could be an underestimate. There is evidence that these diseases are as common as inflammatory bowel diseases (IBD)^{3,4}
- Current treatment options, such as diet restriction and corticosteroids, have limited efficacy and/or are inappropriate for chronic use
- New therapies are needed

Figure 2. High Rate of De Novo Detection of EG and/or EoD in the ENIGMA Study Suggests a Significant Underdiagnosis of These Diseases⁵



- Lirentelimab is a humanized monoclonal antibody against siglec-8, an inhibitory receptor found only on mature eosinophils and mast cells
- Engagement of siglec-8 by lirentelimab induces:
 - Antibody-dependent cell-mediated cytotoxicity (ADCC, blood) and apoptosis (tissue) of eosinophils
 - Inhibition of mature mast cells in tissue
- EG and/or EoD have been described as rare conditions found in atopic individuals with increased peripheral eosinophils and/or total IgE. 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
- Here, we conducted a prospective study to evaluate symptomatic patients for prevalence of EG and/or EoD and to characterize their clinical presentation to inform diagnostic protocols

Figure 3. Significant Symptom Reduction in the ENIGMA Study⁵



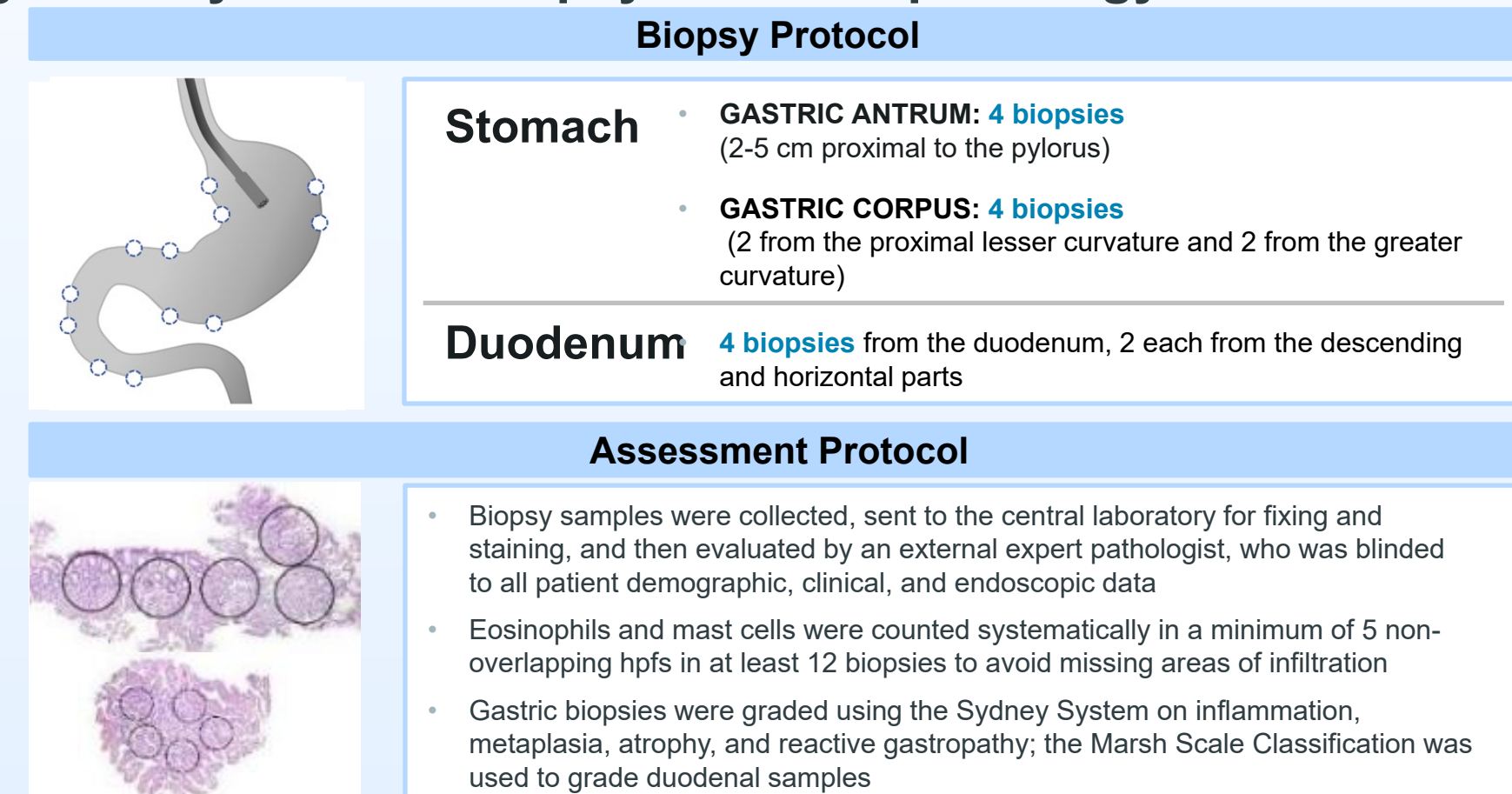
METHODS

- Prospective, multi-center study to assess the prevalence of EG and/or EoD in patients with chronic functional GI symptoms
- Patients qualified for screening with:
 - 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 irritable bowel syndrome (IBS) or functional dyspepsia (FD), indicating chronic symptoms
- A study of healthy volunteers (controls) was conducted for comparison
- Primary endpoints included proportion of 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

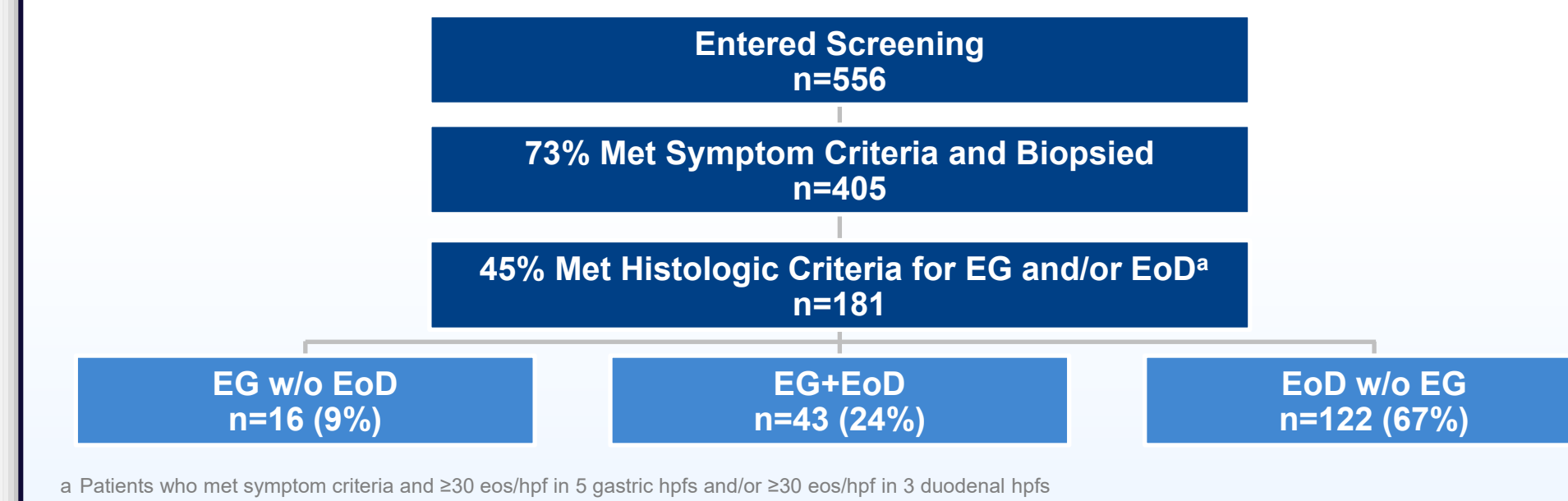
- Developed in accordance with FDA guidance on development of patient-reported outcome (PRO) measurements
- Captures patients' daily GI symptoms
- Measures each symptom on a scale of 0-10 for the following:
 - Abdominal pain
 - Loss of appetite
 - Nausea
 - Abdominal cramping
 - Vomiting
 - Bloating
 - Early satiety
 - Diarrhea
- Patients had daily scores of ≥ 3 (on a scale from 0 to 10) for any individual symptom and Total Symptom Scores (TSS) ≥ 10
- Controls had an average daily score ≤ 1 for all symptoms and no daily score ≥ 3 , on any day, for any symptom

Figure 4. Systematic Biopsy and Histopathology Assessment



RESULTS

Figure 5. High Prevalence of EG and/or EoD in Patients with Chronic 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

Figure 6. Proportion of Patients and Controls Meeting Blood Eosinophil or IgE Thresholds

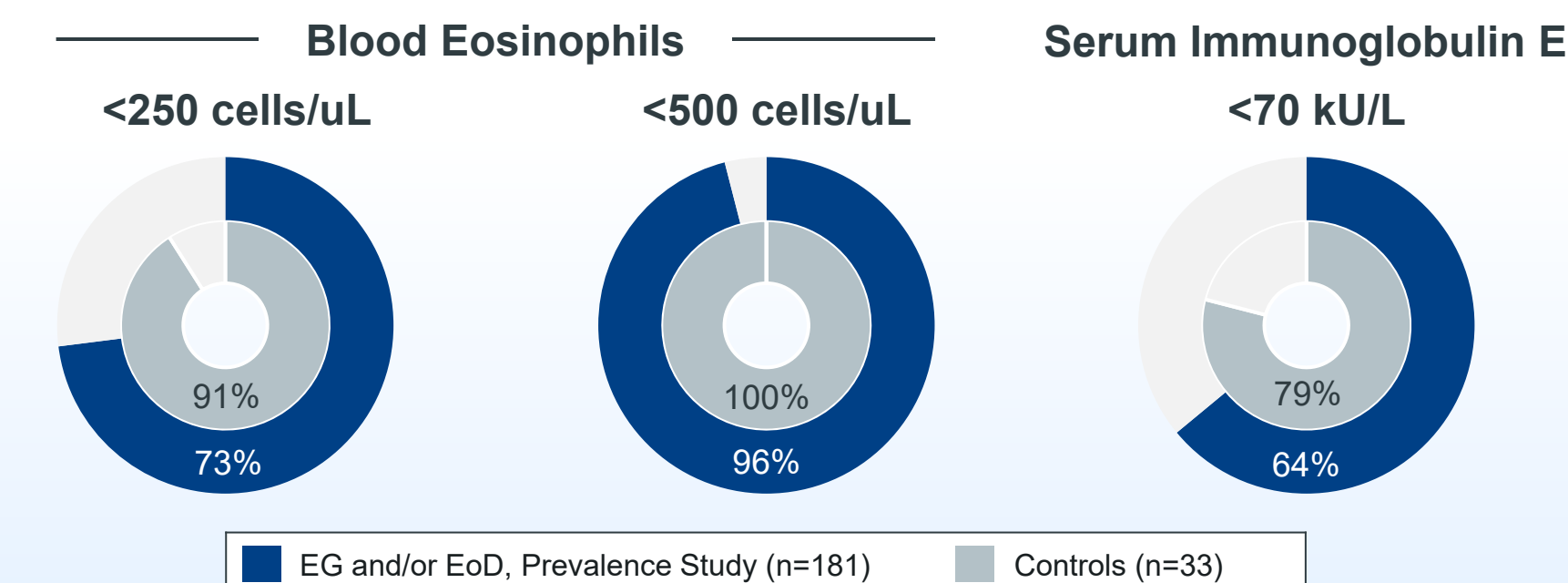


Table 1. Features of Patients with EG and/or EoD and Controls

Patient Characteristics	Met Histologic ^a Criteria for EG and/or EoD n=181	Controls n=33	
Mean age, years (range)	45 (19-78)	34 (18-51)	
Female sex, %	73%	39%	
White, %	85%	100%	
Weight, median, kg	83	80	
Blood eosinophils	Cells/ μ L, median (IQR)	170 (100-250)	70 (50-150)
	Blood eos ≥ 500 cells/ μ L, %	4%	0%
	Blood eos ≥ 1500 cells/ μ L, %	0%	0%
Immunoglobulin E	kU/L, median (IQR)	34 (14-103)	18 (9-60)
TSS [0-80], mean \pm SD	31.3 \pm 11.2	0.1 \pm 0.2	
History of	GI symptoms ^b , mean years	11	-
	GERD, IBS, FD, and/or EoE, %	93%	0
	GERD, %	65%	0
	IBS, %	55%	0
	FD, %	15%	0
	Atopy ^c , %	48%	15%
	EoE, %	2%	0%

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

Figure 7. Blood Eosinophilia and IgE in Patients and Controls

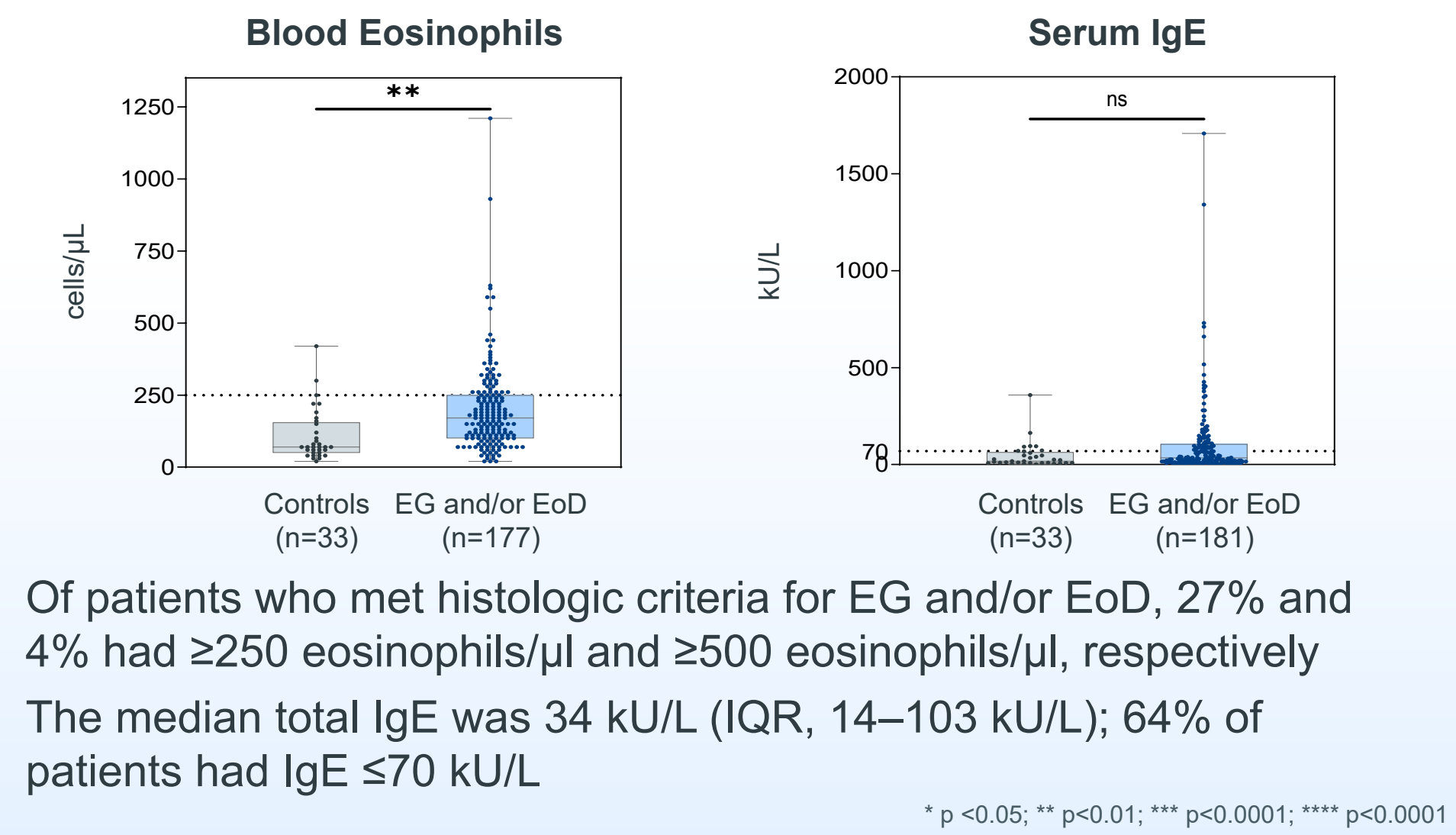
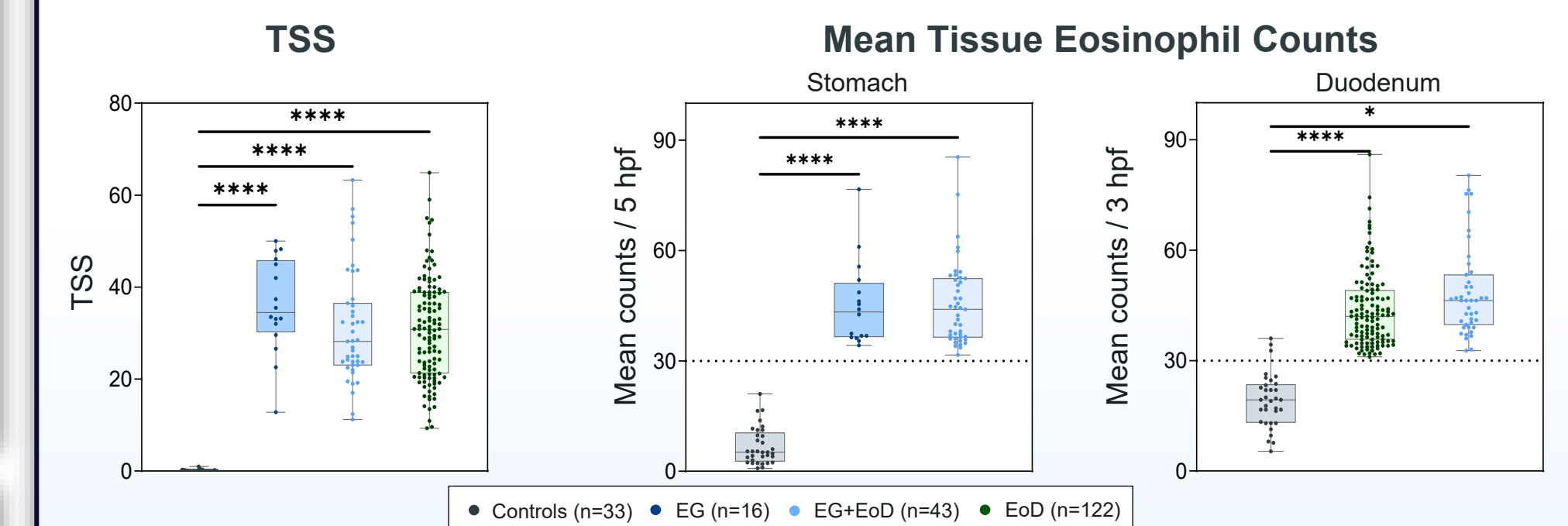


Figure 8. TSS and Mean Eosinophil Counts in Patients vs Controls



- 45% (181/405) of patients and 6% (2/33) of controls^a met histologic criteria for EG and/or EoD (odds ratio, 12.52; 95% CI, 3.0–53.0; p < 0.001)

^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/DISCUSSION

- Systematic endoscopy and biopsy of patients with moderate-severe chronic functional GI symptoms led to a high discovery rate (45%) of EG and/or EoD
- Most newly identified patients did not have peripheral eosinophilia or elevated IgE, indicating that these are not markers of EG and/or EoD
- EG and EoD patients had significantly higher symptom scores and tissue eosinophil counts compared to controls
- These results suggest EG and EoD may have a spectrum of different disease types with differing levels of peripheral eosinophils and IgE
- Further studies of EG and EoD are required to better understand their clinical, endoscopic, and histologic features including biomarkers