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ORIGINAL RESEARCH

Retrospective Evaluation of pH-Impedance, Manometry, and Endoscopy Patients with Hypersensitive Esophagus and Its Treatment Outcomes

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ABSTRACT

Hypersensitive esophagus (HE) is a clinical entity characterized by typical reflux symptoms despite normal acid exposure time (AET) on pH-impedance monitoring. Understanding its pathophysiology and optimizing management remain challenging. This retrospective study evaluated clinical characteristics, endoscopic and functional findings, symptom-reflux association, and treatment outcomes in 142 patients who met the Lyon Consensus 2.0 criteria for HE (AET <4%, symptom index [SI] and/or symptom association probability [SAP] positive). Endoscopic findings were classified according to the Los Angeles classification, and high-resolution manometry results were interpreted based on the Chicago Classification v4.0. SI and SAP. values were calculated. The cohort was predominantly female (70.4%) with a mean age of 42.2 ± 11.8 years. Heartburn (83.1%) and regurgitation (76.1%) were the most frequent. Endoscopy was normal in most, with only 7.0% showing mild esophagitis. Mean AET was 1.56% ± 0.99%. No significant differences were found in reflux burden, motility, or baseline impedance between symptom-based subgroups. SI positivity was linked to increased reflux time and diminished lower esophageal sphincter tone; SAP positivity correlated with reduced distal contractile integral. Overall treatment response was 37.3%, while second-line therapies—particularly selective serotonin reuptake inhibitors (SSRIs)—achieved a high success rate of 98.9% among the 89 patients who did not respond to initial treatment. HE is a distinct disorder with minimal acid burden and functional alterations, poorly captured by conventional metrics. Symptom association indices may aid diagnosis but cannot guide treatment alone. Neuromodulatory approaches, particularly SSRIs, appear more effective than acid suppression, highlighting the importance of individualized, perception-targeted strategies.

Keywords: Hypersensitive esophagus. pH-impedance monitoring. Esophageal motility. High-resolution esophageal manometry. Baseline mucosal impedance. Symptom association probability.

Hipersensitif Özofaguslu Hastalarda pH-İmpedans, Manometri ve Endoskopi Bulgularının Retrospektif Değerlendirilmesi ve Tedavi Sonuçları

ÖZET

Hipersensitif özofagus (HE), pH-impedans izleminde normal asit maruziyeti süresine (AET) rağmen tipik reflü semptomlarıyla karakterize klinik bir tablodur. Patofizyolojisinin anlaşılması ve tedavi optimizasyonu halen zorluklar içermektedir. Bu retrospektif çalışmada, Lyon Konsensusu'na göre HE tanısı alan (AET <%4, semptom indeksi [SI] ve/veya semptom ilişki olasılığı [SAP] pozitif) 142 hastanın klinik özellikleri, endoskopik ve fonksiyonel bulguları, semptom-reflü ilişkisi ve tedavi sonuçları değerlendirildi. Los Angeles sınıflamasına göre endoskopik bulgular, Chicago sınıflaması v4.0'a göre yüksek çözünürlüklü manometri sonuçları analiz edildi. SI ve SAP değerleri hesaplandı. Kohortun %70,4'ü kadın olup, yaş ortalaması 42,2 ± 11,8 yıl idi. En sık görülen semptomlar yanma (%83,1) ve regürjitasyon (%76,1) idi. Endoskopik incelemede çoğunlukla normal bulgu saptanırken, %7,0 olguda hafif özofajit görüldü. Ortalama AET %1,56 ± 0,99 idi. Semptom grupları arasında reflü yükü, motilite veya bazal mukoza empedansında anlamlı farklılık bulunmadı. SI pozitifliği artmış reflü süresi ve düşük alt özofagus sfinkter basıncı ile ilişkilendirildi; SAP pozitifliği ise distal kontraktil integral azalması ile korelasyon gösterdi. Genel tedavi yanıtı %37,3 iken, özellikle seçici serotonin geri alım inhibitörleri (SSRI) ile uygulanan ikinci basamak tedaviler, ilk tedaviye yanıt vermeyen 89 hastada %98,9 oranında yüksek bir başarı sağlamıştır. HE, minimal asit yükü ve fonksiyonel değişikliklerle seyreden, geleneksel parametrelerle iyi yansıtılamayan özgün bir hastalık grubudur. Semptom-reflü ilişki indeksleri tanıda yardımcı olabilir ancak tedavi yönlendirmesinde tek başına yeterli değildir. Nöromodülatör tedaviler, özellikle SSRI'lar, asit baskılayıcı tedavilere kıyasla daha etkili görünmekte olup, bireyselleştirilmiş ve algıya yönelik tedavi stratejilerinin önemini vurgulamaktadır.

Anahtar Kelimeler: Hipersensitif özofagus. pH-impedans izleme. Özofagus motilitesi. Yüksek çözünürlüklü özofagus manometrisi. Bazal mukoza empedansı. Semptom ilişki olasılığı.

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Hypersensitive esophagus (HE) is a condition where patients experience esophageal pain or discomfort despite normal endoscopic findings and normal acid exposure levels. Esophageal pH monitoring, a key diagnostic tool, typically shows normal acid exposure times in HE patients, distinguishing it from classic gastroesophageal reflux disease (GERD). However, during pH monitoring, there is often a positive symptom association between reflux episodes and patient-reported symptoms, indicating that even normal levels of acid can trigger hypersensitive responses in the esophagus[1,2]. Recent epidemiological studies estimate that HE accounts for approximately 20–40% of patients presenting with typical GERD symptoms despite normal acid exposure, underscoring its clinical relevance and diagnostic challenge[3,4].

According to the Lyon Consensus 2.0, an acid exposure time (AET) below 4% is considered normal. In the absence of erosive esophagitis or pathological reflux, symptom generation is attributed primarily to increased esophageal sensory perception rather than acid burden itself[5]. This entity overlaps with previously classified conditions such as functional heartburn (FH) and non-erosive reflux disease (NERD). The Rome IV criteria further refine diagnosis by incorporating positive symptom-reflux association metrics—such as symptom index (SI) and symptom association probability (SAP)—in patients with normal AET, thereby enabling a more precise identification of HE[6].

The pathophysiological mechanisms underlying HE remain incompletely understood and are considered multifactorial. While proton pump inhibitors (PPIs) are effective in most patients with acid-related GERD, many individuals with HE experience refractory symptoms despite adequate acid suppression[7]. These persistent symptoms are believed to be mediated by mechanisms beyond acid exposure, including visceral hypersensitivity, subtle abnormalities in esophageal motility, disruption of mucosal integrity, and central sensitization[8,9]. High-resolution esophageal manometry (HREM), interpreted according to the Chicago Classification v4.0, allows detailed evaluation of esophageal motor function and helps distinguish primary motility disorders from sensory-driven phenotypes[10].

Neuromodulators such as selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants may alleviate symptoms in PPI-refractory patients by modulating central pain pathways[8,9]. Nevertheless, their precise role and predictors of response in HE remain unclear. Despite advances in diagnostics, there is a lack of reliable clinical or physiological markers to predict treatment response in HE, highlighting the need for comprehensive phenotyping and tailored strategies.

This study focuses on a homogeneous cohort of HE patients characterized by normal or IEM and normal acid exposure, integrating clinical, endoscopic, manometric, and reflux parameters to identify predictors of treatment response. This retrospective analysis aims to (1) characterize the clinical, endoscopic, manometric, and reflux profiles of patients with HE (AET < 4%), (2) investigate associations among diagnostic parameters, and (3) evaluate treatment responses to PPI- and SSRI-based therapies. Insights from this study may facilitate personalized treatment approaches and improve outcomes in this diagnostically complex and therapeutically challenging GERD subgroup.

Material and Method

This retrospective study included consecutive adult patients evaluated for typical reflux symptoms at the Kocaeli University Motility Unit between January 2021 and June 2025, minimizing selection bias. Symptom severity and duration were assessed using the standardized GERD-Q questionnaire[11]. Demographic data, symptom characteristics, and comorbidities were recorded.

Patients presenting with heartburn, regurgitation, or chest pain and physiological acid exposure (AET<4%) on 24-hour pH-impedance monitoring (MII-pH) were included in accordance with the Lyon Consensus 2.0[5]. FH was defined as AET<4%, negative SAP, negative SI, and no LA grade B or higher esophagitis on endoscopy, based on Lyon 2.0 and Rome IV criteria[5,6].

Endoscopic findings were classified using the Los Angeles (LA) grading system[12]. For *Helicobacter pylori (H. Pylori)* detection and mucosal assessment, biopsies were obtained per the Sydney protocol: two from the antrum, one from the incisura angularis, and one each from the lesser and greater curvatures of the corpus[13]. Samples (~3×3 mm) were collected using single-use forceps (Endo-Flex®, GmbH, Voerde, Germany), and endoscopies were performed with a FUJIFILM EG-760R gastroscope (FUJIFILM Corporation, Tokyo, Japan).

MII-pH monitoring was conducted using a single-use impedance catheter (VersaFlex-Z®, Medtronic, Minneapolis, MN, USA), with the distal pH sensor placed 5 cm above the lower esophageal sphincter (LES). Calibration was performed with pH 1.0 and 7.0 buffers. Placement was guided by endoscopic identification of the Z-line and confirmed fluoroscopically. Data were recorded for 22–24 hours.

Mean nocturnal baseline impedance (MNBI) was measured manually by a single experienced physician to reduce interobserver variability. MNBI was calculated from the Z5 channel (5 cm above LES) during three 10-minute nocturnal periods (~1:00, 2:00,

and 3:00 a.m.) free of swallowing or reflux, following established protocols[2,5].

Symptom association with reflux episodes (REs) was evaluated using SI and SAP, with positivity defined as SI ≥ 50% and SAP > 95%, per Lyon 2.0 and Rome IV criteria[5,6].

Esophageal motility was assessed using a water-perfused HREM system (Medtronic Polygram Net™, v4.01; Tonsbakken, Denmark). The catheter had five sensors spaced 1 cm apart distally and additional sensors at 2 cm intervals proximally. Calibration covered 0–50 mmHg. Motility recordings were done after ≥8 hours of fasting. Patients performed ten 5 mL water swallows at room temperature; swallows with artifacts (e.g., coughing, belching, multiple swallows) were excluded.

Manometric findings were interpreted per the Chicago Classification v4.0[10]. IEM was diagnosed when >70% of swallows were ineffective or >50% showed weak contractions. Peristaltic breaks >5 cm were considered major, indicating impaired contractility.

Treatment allocation was determined based on the predominant symptom profile and the presence of psychiatric comorbidities. Patients presenting with pain-predominant or hypersensitivity-related symptoms and/or documented psychiatric comorbidities (e.g., anxiety, depression) were primarily managed with SSRIs, whereas those without such features received PPIs and/or antacids as first-line therapy.

Treatment response was defined as a ≥50% reduction in symptom frequency and/or intensity, assessed using a standardized symptom questionnaire derived from the GERD-Q, in combination with the patient's subjective report of global symptom improvement ("much improved" or "completely resolved").

Patients who were refractory to PPI therapy received selective SSRIs as second-line treatment. SSRIs were administered for a minimum duration of three months, consistent with their expected therapeutic onset period. Due to the retrospective design of the study, detailed data on drug dosages, adherence, and side effect profiles were not uniformly available and were therefore not included in the analysis.

Ethics approval was obtained from the Non-Interventional Clinical Research Ethics Committee of Kocaeli University (Approval No: KU GOKAEK-2025/17/22, Project No: 2025/431)

Statistical Analysis

This retrospective study, conducted from 2021 to 2025, included all 142 eligible cases meeting the inclusion and exclusion criteria, as the relatively modest sample size precluded a priori power analysis without compromising statistical power.

Data were analyzed using IBM SPSS Statistics version 29.0 (IBM Corp., Armonk, NY, USA). Normality of continuous variables was tested with Kolmogorov–Smirnov and Shapiro–Wilk tests. Normally distributed data are presented as the mean ± standard deviation (SD), and non-normal data are presented as the median (interquartile range). Categorical variables are shown as frequencies and percentages. Between-group comparisons used Student's t-test for normal data and Mann–Whitney U test for non-normal data. Chi-square or Fisher's exact test was applied for categorical variables as appropriate. Correlations among reflux parameters, symptom association indices, manometric findings, and treatment response were evaluated using Pearson's correlation for parametric and Spearman's rank correlation for non-parametric data. Multiple comparisons were adjusted by Bonferroni correction when needed. A two-tailed p-value < 0.05 was considered statistically significant.

Inclusion and Exclusion Criteria

Adults (≥18 years) with typical reflux symptoms (heartburn, regurgitation, or non-cardiac chest pain lasting ≥3 months) who were assessed by GERD-Q were included. Patients had physiological acid exposure (AET <4%) per Lyon Consensus 2.0 and positive symptom–reflux association (SI ≥50% and/or SAP >95%) per Rome IV criteria[5,6]. The analysis included only patients who had at least three symptom episodes recorded, allowing for the evaluation of SAP.

Exclusion criteria included pathological acid exposure (AET≥4%), LA grade B-D esophagitis, Barrett's esophagus, peptic ulcer, hiatal hernia>2 cm, major motility disorders per Chicago Classification v4.0 (achalasia, EGJOO, distal spasm, jackhammer esophagus, absent peristalsis), and FH (normal AET, negative symptom-reflux association).

Additional exclusions were prior upper GI surgery; use of medications affecting motility or sensitivity within two weeks (opioids, TCAs, CCBs, prokinetics, neuromodulators); severe psychiatric or neurological diseases; uncontrolled systemic conditions (e.g., diabetic autonomic neuropathy); incomplete or poor-quality MII-pH or manometry studies; and pregnancy or lactation.

Results

A retrospective analysis included 142 patients with HE, predominantly female (70.4%, n=100), mean age 42.25 ± 11.80 years, and mean BMI 23.11 ± 3.85 kg/m². Most (78.9%, n=112) had normal BMI (18.0–24.9), 13.4% (n=19) were overweight, 6.3% (n=9) obese, and 1.4% (n=2) underweight (Table I). Comorbidities were absent in 52.8% (n=75); 47.2%

(n=67) had at least one, including psychiatric disorders (23.9%, n=34), hypertension (14.1%, n= 20), diabetes mellitus (8.5%, n=12), asthma/bronchitis (5.6%, n=8), and hypothyroidism (5.6%, n=8). Most patients were non-smokers (86.6%, n=123), with 9.9% current and 3.5% former smokers; alcohol use was rare (2.1%, n=3).

Table I. Demographic and clinical characteristics of patients with hypersensitive esophagus

Parameter	n= 142
Age (years)	42.25 ± 11.80
Female	100 (70.4%)
Male	42(29.6%)
BMI (kg/m²)	23.11 ± 3.85
Underweight	2 (1.4%)
Normal weight	112 (78.9%)
Overweight	19 (13.4%)
Obese	9 (6.3%)
Comorbidity	67 (47.2%)
Anxiety /depression	34 (23.9%)
Current Smokers	14 (9.9%)
Quit Smoking	5 (3.5%)
Alcohol Consumption	3 (2.1%)
Heartburn	118 (83.1%)
Regurgitation	108 (76.1%)
Chest Pain	35 (24.6%)
Dysphagia	26 (18.3%)

Values are presented as mean ± standard deviation for continuous variables and number (percentage) for categorical variables. BMI categories were defined as follows: Underweight, BMI < 18.5 kg/m²; normal weight, BMI 18.5–24.9 kg/m²; overweight, BMI 25–29.9 kg/m²; obese, BMI ≥ 30 kg/m².Abbreviations: BMI, body mass index; n, number of patients.

Symptom duration was longest for cough (36.51 ± 58.21 months) and heartburn (33.23 ± 36.31 months). Heartburn affected 83.1% (n= 118), with frequencies: <1/week (17.6%), ~1/week (60.6%), 2–3/week (16.9%), and ≥4/week (4.9%). Severity was mostly moderate (74.6%), with mild (8.5%), severe (16.1%), and very severe (0.8%); 16.9% data missing.

Regurgitation was present in 76.1% (n= 108), frequencies: <1/week (30.5%), once weekly (43.3%), 2–3 times/week (19.9%), and ≥4 times/week (6.4%). Impact on daily life was mild in 19.4%, moderate in 58.3%, and severe in 22.2%; 23.9% missing data.

Chest pain occurred in 24.6% (n= 35), with weekly frequencies: once (14.1%), 2–3 times (5.6%), and ≥4 times (1.4%). Dysphagia was reported by 18.3% (n= 26) with similar frequency distribution. Stomach pain affected 38.7% (n=55), mostly once weekly (28.9%).

Other symptoms included belching (24.6%), nausea (20.4%), vomiting (13.4%), prolonged hiccups (>3 months, 1.4%), chronic cough (>3 months, 7.7%), hoarseness (8.5%), chronic pharyngitis/laryngitis (2.8%), and abdominal bloating (19.0%).

Endoscopically, 31.0% (n=44) had hypotensive gastroesophageal junction, 3.5% (n=5) hiatal hernia (<2 cm), and 7.0% (n=10) mild esophagitis (LA grade A); others were normal. *H. pylori* infection was found in 28.2% (n=40), negative in 71.8% (n=102).

The study included 142 patients with HE. The mean AET was 1.56 ± 0.99%, with upright reflux (2.02 ± 1.48%) exceeding supine (0.70 ± 1.04%). Postprandial reflux time averaged 2.34 ± 1.83%. All patients had AET <4%. Mean DeMeester score was 6.77 ± 3.87. SI was positive in 28.2%, SAP in 89.4%. Mean SI was 32.18 ± 25.46%, SAP 97.16 ± 9.40% (Table II). All had <40 reflux episodes. MNBI was >2500 Ω in 78.9% and 1500–2500 Ω in 21.1%.

Table II. Summary of esophageal physiological parameters in patients with hypersensitive esophagus based on 24-hour ımpedance-pH monitoring and high-resolution manometry

Parameter	
AET	1.56 ± 0.99
Upright Reflux Time	2.02 ± 1.48
Supine Reflux Time	0.70 ± 1.04
Postprandial Reflux Time	2.34 ± 1.83
SI	32.18 ± 25.46
SAP	97.16 ± 9.40
DeMeester Score	6.77 ± 3.87
Total REs	22.04 ± 10.52
MNBI (Ω)	3481.94 ± 1151.06
Upright REs	18.16 ± 11.02
Supine REs	3.54 ± 6.72
Postprandial RE	16.05 ± 9.98
Bolus Exposure Time Upright	0.97 ± 1.83
Bolus Exposure Time Supine	0.17 ± 0.16
Supine IRP (mmHg)	8.05 ± 5.45
LES Resting Pressure (mmHg)	18.16 ± 11.01
Supine DCI (mmHg·s·cm)	836.44 ± 678.85
CFV (cm/s)	4.91 ± 1.63
Peristaltic Break (cm)	4.91 ± 1.63
Supine DL (sec)	7.22 ± 4.92

Abbreviations: AET, acid exposure time; SI, symptom ındex; SAP, symptom association probability; RE, reflux episodes; MNBI, mean nocturnal baseline impedance; IRP, integrated relaxation pressure; LES, lower esophageal sphincter; DCI, distal contractile ıntegral; CFV, contractile front velocity; DL, distal latency. Values are expressed as mean ± standard deviation. Data were collected through 24-hour impedance-pH monitoring and high-resolution manometry in patients with hypersensitive esophagus.

HREM was normal in 71.1%, with IEM observed in 28.9%. LES resting pressure averaged 18.16 ± 11.01 mmHg; supine IRP (integrated relaxation pressure), 8.05 ± 5.45 mmHg; DCI, 836.44 ± 678.85

mmHg·s·cm; DL, 7.22 ± 4.92 s; and peristaltic break length, 4.91 ± 1.63 cm (Table II).

Subgroup analysis found no significant differences in reflux or motility metrics between patients with and without heartburn, except fewer supine reflux episodes (p= 0.040) and minor differences in peristaltic break length (p= 0.044) among those with heartburn. Heartburn prevalence was similar regardless of motility findings (p= 1.000).

Among those with regurgitation (n= 108), LES resting pressure was significantly lower (p= 0.016), but other MII-pH and HREM parameters did not differ. Regurgitation was not associated with SI, SAP, MNBI, or motility findings (all p> 0.09).

Chest pain and dysphagia showed no significant associations with SI, SAP, MNBI, or manometry (all p>0.23), although chest pain was linked to higher LES pressure (p=0.012).

Patients in the SI positive group exhibited significantly higher total AET (2.25 ± 0.95 vs. 1.30 ± 0.87, p< 0.001), upright AET (2.88 ± 1.49 vs. 1.69 ± 1.34, p<0.001), and postprandial AET (2.40 ± 1.81 vs. 2.08 ± 1.94, p<0.001) compared to SI negative patients. DeMeester score and the number of reflux episodes (RE), including upright RE, were also significantly elevated in the SI positive group (p<0.001 and p=0.010, respectively). Additionally, the LES pressure was significantly lower in the SI positive group (17.80 ± 7.62 mmHg) compared to the SI negative group (21.46 ± 8.69 mmHg, p=0.011), suggesting an association between reduced LES function and symptom generation.

In contrast, among SAP groups, SI (p<0.001), SAP values (p< 0.001), and DCI (878 ± 702 vs. 483 ± 236 mmHg·s·cm, p=0.019) were significantly higher in SAP positive patients. However, LES pressure did not differ significantly between SAP negative and SAP positive groups (17.73 ± 8.63 vs. 20.7 ± 8.49 mmHg, p= 0.214). No statistically significant differences were observed in MNBI or distal latency (DL) between groups based on either SI or SAP classification (Table III). A strong association was observed between SI and SAP status (p<0.001).

Initial treatments included PPI alone (34.5%), alginate alone (16.2%), PPI + alginate (39.4%), SSRI alone (7.0%), and PPI + SSRI (2.8%) (Table IV). Symptomatic improvement was reported in 37.3%. Among non-responders (62.7%), second-line treatments (mostly SSRI-based) achieved a 98.9% response rate (Table V). Treatment type showed no significant association with SI, SAP, or MNBI categories (all p>0.21). The most common regimen across all groups was combined PPI and alginate therapy, followed by PPI monotherapy. SSRIs were used infrequently and without a clear pattern based on SI, SAP, or MNBI subgroup.

Treatment distribution differed significantly by manometric status (p= 0.028). Patients with normal motility were more frequently treated with combination therapy (44.6%) or PPI monotherapy (35.6%), whereas those with IEM were more likely to receive either PPI monotherapy (31.7%) or alginate alone (29.3%). SSRI use was higher in the IEM group (12.2%) compared to those with normal motility.

Although SI values were numerically highest in the alginate group (36.54 ± 22.87) and lowest in the SSRI group (25.84 ± 20.22), differences in DeMeester scores and MNBI were not statistically significant

Table III. Comparison of esophageal physiological parameters between symptom index (SI) negative and positive groups, and symptom association probability (SAP) negative and positive groups

Parameter	SI Negative (n= 102)	SI Positive (n= 40)	*p*-value	SAP Negative (n= 15)	SAP Positive (n= 127)	*p*-value
AET	1.30 ± 0.87	2.25 ± 0.95	< 0.001	2.15 ± 1.25	1.50 ± 0.94	0.045
Upright AET	1.69 ± 1.34	2.88 ± 1.49	< 0.001	2.64 ± 1.76	1.95 ± 1.43	0.162
Supine AET	0.62 ± 1.01	0.88±1.09	0.063	0.90±1.07	0.67± 1.04	0.380
Postprandial AET	2.08 ± 1.94	2.40 ± 1.81	< 0.001	3.55 ± 2.66	2.20 ± 1.67	0.380
SI	19.16 ± 13.66	65.40 ± 16.88	< 0.001	63.91 ± 19.32	28.44 ± 23.45	< 0.001
SAP	98.76 ± 1.98	93.07 ±16.89	0.330	81.41 ± 23.89	99.02 ± 1.55	< 0.001
DeMeester	5.89 ± 3.55	9.03 ± 3.77	< 0.001	6.64 ± 3.79	7.89 ± 4.44	0.300
RE	18.46 ± 11.01	22.84 ± 10.11	< 0.001	22.84 ± 10.11	23.93 ± 8.45	0.445
Upright RE	16.59± 11.41	22.18 ±8.87	0.010	17.93 ± 9.80	18.67 ± 7.97	0.546
Postprandial RE	2.08 ± 1.94	2.40 ± 1.81	0.040	16.11 ± 10.33	15.54 ± 6.47	0.722
Upright BET	0.86 ± 1.41	1.25 ± 2.61	0.017	0,73 ± 0,46	1,00 ±1,92	0.702
MNBI (Ω)	3494 ± 1194	3450 ± 1044	0.942	3521 ± 1189	3477±1151	0.737
LESpressure (mmHg)	21.46 ± 8.69	17.80 ± 7.62	0.011	17.73 ± 8.63	20.7 ± 8.49	0.214
DCI (mmHg·s·cm)	894 ± 740	689 ± 464	0.194	483 ± 236	878 ± 702	0.019
DL (sec)	7.29 ± 5.77	7.03 ± 1.17	0.105	6.99 ± 1.23	7.24 ± 5.19	0.632

Abbreviations: AET, acid exposure time; SI, symptom index; BET, bolus exposure time; SAP, symptom association probability;RE, reflux episode; LES, lower esophageal sphincter; MNBI, mean nocturnal baseline impedance;DCI, distal contractile integral; DL, distal latency. Values are presented as mean ± standard deviation (SD).

Table IV. Comparison of esophageal physiological parameters among treatment groups.

Parameter	PPI (n= 49)	Alginates (n= 23)	PPI + Alginates (n= 56)	SSRI (n= 14)	*p* value
AET	1.41 ± 1.07	1.50 ± 0.82	1.65 ± 0.99	1.87 ± 0.97	0.295
Upright AET	1.78 ± 1.55	2.17 ± 1.22	2.06 ± 1.47	2.51 ± 1.64	0.308
Supine AET	0.73 ± 1.09	0.49 ± 0.51	0.76 ± 1.21	0.69 ± 0.80	0.789
Postprandial AET	2.13 ± 2.09	2.41 ± 1.36	2.44 ± 1.87	2.57 ± 1.49	0.377
SI	28.88 ± 23.41	36.54 ± 22.87	34.87 ± 29.02	25.84 ± 20.22	0.396
SAP	95.05 ± 15.25	98.60 ± 3.34	98.17 ± 3.32	98.85 ± 1.49	0.231
DeMeester Score	6.23 ± 4.19	7.10 ± 3.00	6.81 ± 4.08	7.97 ± 3.05	0.268
RE	20.22 ± 10.54	25.30 ± 10.02	21.61 ± 10.76	24.71 ± 9.52	0.177
MNBI (Ω)	3546 ± 1176	3816 ± 1337	3371 ± 1112	3153 ± 790	0.507
Upright RE	15.29 ± 8.48	20.66 ± 11.04	18.00 ± 11.20	24.79 ± 14.97	0.043
Supine RE	3.62 ± 6.23	2.55 ± 3.06	3.75 ± 8.33	4.09 ± 5.87	0.839
Postprandial RE	12.86 ± 8.05	18.27 ± 8.52	16.50 ± 9.74	21.79 ± 15.26	0.022
Upright BET	0.64 ± 0.53	1.70 ± 3.55	0.92 ± 1.66	1.11 ± 0.85	0.136
Supine BET	0.18 ± 0.18	0.22 ± 0.27	0.14 ± 0.09	0.17 ± 0.12	0.626
Supine IRP (mmHg)	7.51 ± 5.43	6.52 ± 4.79	8.38 ± 5.33	11.14 ± 6.16	0.071
LES Pressure (mmHg)	18.98 ± 8.22	19.65 ± 10.00	20.45 ± 8.29	26.71 ± 5.38	0.029
Supine DCI (mmHg·s·cm)	939 ± 795	634 ± 894	882 ± 490	629 ± 359	0.011
CFV (cm/s)	5.13 ± 1.95	5.04 ± 1.98	4.78 ± 1.24	4.46 ± 1.17	0.702
PB (cm)	3.33 ± 2.85	3.50 ± 2.35	2.82 ± 2.62	3.11 ± 2.02	0.817

Abbreviations: PPI, Proton pump inhibitor; SSRI, selective serotonin reuptake inhibitor; AET, acid exposure time; SI, symptom index; SAP, symptom association probability; DeMeester score; RE, reflux episodes; MNBI, mean nocturnal baseline impedance; BET, bolus exposure time; IRP, integrated relaxation pressure; LES, lower esophageal sphincter; DCI, distal contractile integral; CFV, contractile front velocity; PB, peristaltic break. Note: Values are presented as mean ± standard deviation (SD).

among treatment subgroups. Notably, LES resting pressure was significantly elevated in the SSRI group (26.71 ± 5.38 mmHg; p= 0.029), and DCI varied across therapies (p= 0.011), highest in the PPI group (939.14 ± 794.0 mmHg·s·cm) and lowest in the SSRI (629.29 ± 359.0 mmHg·s·cm) and alginate groups.

Table V. Treatment modalities and responses in patients with hypersensitive esophagus

Category	n (%)
Initial Treatment	
PPI alone	49 (34.5%)
Alginate alone	23 (16.2%)
PPI + Alginate	56 (39.4%)
SSRI alone	10 (7.0%)
PPI + SSRI	4 (2.8%)
Treatment Response	
Responders	53 (37.3%)
Non-responders	89 (62.7%)
Second-line Treatment (Non-responders, n=89)	
PPI + Alginate	21 (23.6%)
SSRI	27 (30.3%)
PPI + SSRI	41 (46.1%)
Response to Second-line Treatment (n=89)	
Responders	88 (98.9%)
Non-responders	1 (1.1%)

Abbreviations: PPI, Proton Pump Inhibitor; SSRI, Selective Serotonin Reuptake Inhibitor; Responders, patients showing clinical improvement; Non-responders, patients without clinical improvement. Note: Values are presented as number of patients (n) and percentage (%).

Treatment response among patients with HE was not associated with SI positivity (42.5% vs. 35.3%; p = 0.446), SAP status (38.6% vs. 26.7%; p = 0.414), MNBI levels (p=0.675), or motility pattern (p=0.703).

However, responders demonstrated significantly lower reflux burden and improved esophageal metrics. Compared to non-responders, they had reduced upright (16.42 ± 3.76 vs. 21.10 ± 10.01; p=0.029), supine (2.62 ± 3.76 vs. 5.10 ± 9.73; p=0.042), and postprandial REs (14.44 ± 8.39 vs. 18.76 ± 11.79; p = 0.039), lower supine bolus exposure time (0.15 ± 0.14% vs. 0.20 ± 0.20%; p=0.026), and significantly reduced supine IRP (4.69 ± 1.73 mmHg vs. 7.31 ± 5.47 mmHg; p=0.009). Manometric pattern (normal vs. IEM) was not predictive of response (p=0.759). The detailed comparison of esophageal physiological parameters among different treatment groups is presented in Table IV, while treatment modalities and therapeutic responses in patients with HE are summarized in Table V.

Discussion and Conclusion

In this study, a significant female predominance was observed among patients with HE, with women comprising over two-thirds of the cohort (70.4%). This finding is consistent with prior literature reporting a higher prevalence of functional esophageal disorders in females[14]. While the underlying mechanisms remain uncertain, proposed explanations include sex-related differences in visceral pain

perception, hormonal modulation, and heightened psychosocial stress reactivity[15,16].

The mean patient age of 42.25 years suggests that HE typically emerges in early to mid-adulthood. Notably, the majority of patients had a normal body mass index (BMI), with nearly 80% falling within the 18.5–24.9 kg/m² range. This contrasts with gastroesophageal reflux disease (GERD), which is often associated with overweight or obesity[17], implying that BMI may not be a significant risk factor in HE pathogenesis.

Almost half of the patients reported at least one comorbidity, with psychiatric disorders—particularly anxiety and depression—being the most prevalent (23.9%). This aligns with the well-established link between functional esophageal syndromes and psychiatric comorbidities[7]. These findings further support the concept of brain-gut axis dysregulation and heightened visceral sensitivity in HE[4,8], underscoring the importance of a biopsychosocial approach to management.

Tobacco and alcohol use were infrequent in this population (9.9% and 2.1%, respectively), despite their known impact on esophageal motility and mucosal sensitivity[18]. The low prevalence of these exposures suggests they are unlikely to play a central role in symptom generation in HE, at least within this cohort.

H. pylori was detected in 28.2% of patients, which is relatively low compared to its prevalence in the general population. Due to this lower detection rate, the role of *H. pylori* in HE remains uncertain. While some evidence suggests that *H. pylori* may modulate gastric acid secretion and upper gastrointestinal symptoms[19], its clinical relevance in HE requires further investigation. The symptom profile was dominated by classic reflux complaints, particularly heartburn and regurgitation, with heartburn reported by over 80% of patients. These symptoms typically persisted for extended durations—averaging more than 30 months—highlighting the chronic nature of HE. Importantly, most patients demonstrated normal endoscopic findings, reinforcing the classification of HE as a functional esophageal disorder distinct from erosive reflux disease[3].

Despite the frequency of typical symptoms, their severity was generally moderate and not strongly correlated with objective findings such as AET or mucosal injury, consistent with previous research[3,4]. This dissociation between symptom burden and reflux metrics supports the hypothesis that central pain modulation and visceral hypersensitivity play dominant roles in symptom generation[8,9].

Additional symptoms, including chest pain, dysphagia, stomach discomfort, belching, nausea, and vomiting, reflect the broad and overlapping symptom spectrum of HE. Less frequent manifestations—such as chronic cough, hoarseness, and laryngeal irritation—may reflect extra-esophageal reflux or overlap with laryngopharyngeal reflux (LPR), though their specific relationship with HE remains to be clearly defined[20].

Endoscopic evaluation showed that most patients exhibited normal esophageal mucosa, aligning with the HE diagnosis. Mild esophagitis (LA grade A) was present in only 7.0%, and hiatal hernia was identified in 3.5%—rates lower than those typically reported in GERD cohorts. Notably, a hypotensive gastroesophageal junction was observed in a significant subset. While this anatomical alteration alone does not fully explain hypersensitivity, it may facilitate transient reflux events that are perceived more intensely due to heightened sensitivity[4,6–8].

Reflux episodes (REs) were more frequent in the upright position compared to supine, a pattern characteristic of physiologic reflux and commonly seen in functional esophageal disorders. The strong temporal correlation between REs and symptoms, evidenced by a high mean SAP of 97.16%, emphasizes the clinical significance of reflux perception despite the absence of mucosal injury. Although 89.4% of patients exhibited positive SAP, only 28.2% had a positive SI, reflecting differences in these diagnostic metrics' sensitivity and specificity. SAP has been demonstrated to surpass SI in detecting clinically relevant reflux–symptom relationships, particularly in cases with subtle reflux patterns[21].

Most patients had MNBI values exceeding 2500 Ω, indicative of preserved mucosal integrity. Reduced MNBI, linked to impaired mucosal barrier function, is more commonly observed in GERD and NERD, whereas higher impedance supports a functional or hypersensitive esophageal phenotype[22,23].

HREM demonstrated normal esophageal motility in 71.1% of patients, whereas 28.9% exhibited IEM. Although IEM is not specific to GERD or functional disorders, its presence in some HE patients may impair reflux clearance, potentially amplifying symptom perception despite normal acid exposure[24]. Other manometric indices, such as LES resting pressure and DCI, remained within normal limits, indicating preserved esophageal peristalsis and sphincter function in most cases.

These findings collectively reinforce the functional nature of HE, characterized by persistent symptoms despite normal or near-normal structural and physiological assessments. The combination of normal acid exposure, intact mucosal integrity, preserved motility, and positive symptom association substantiates HE as a distinct clinical entity, separate from NERD and FH[4,22,25]. This underscores the importance of symptom-based diagnosis, augmented

by objective tools like MII-pH monitoring and HREM, for accurate identification.

Moreover, the data suggest that symptom generation in HE is primarily driven by visceral hypersensitivity rather than acid-induced mucosal injury. Consequently, conventional acid suppression may be inadequate. Therapeutic approaches focusing on sensory modulation—including neuromodulators, behavioral interventions, and psychogastroenterological treatments—may offer greater benefit[7,8,26]. Such strategies better address the underlying pathophysiology of HE and may improve outcomes in this challenging patient group.

In our cohort, 62.7% of patients experienced no symptomatic improvement with first-line PPI therapy, either alone or combined with alginates, reinforcing evidence that acid suppression frequently fails in functional esophageal disorders, especially when acid exposure is within normal limits[27]. Conversely, neuromodulators—primarily SSRIs—administered as monotherapy or adjunctive to PPIs yielded clinical improvement in 98.9% of patients treated in the second line, consistent with literature supporting their efficacy in modulating central and peripheral pain pathways implicated in visceral hypersensitivity[9,26,27]. These findings underscore the importance of early phenotyping and personalized management beyond acid suppression.

Subgroup analyses revealed no significant differences in reflux parameters—including AET, DeMeester scores, SAP, SI, or MNBI—between patients with and without heartburn, indicating that symptom perception rather than reflux burden differentiates these groups. Although conventional markers such as SI, SAP, MNBI, and motility failed to predict treatment response, quantitative reflux burden and sphincter function correlated more closely with symptomatic improvement in reflux hypersensitivity.

Notably, patients without heartburn showed significantly higher supine reflux episodes (REs) and longer peristaltic breaks, suggesting that esophageal reflux exposure and impaired clearance may occur independently of the perception of typical symptoms such as heartburn. This highlights the discordance between objective reflux measures and clinical presentation in HE. Cross-tabulation confirmed no significant associations between heartburn and key reflux metrics, reinforcing the multifactorial and perceptual nature of this disorder[23]. Importantly, these findings align with the emerging consensus that symptom–reflux correlation metrics—particularly SAP—are critical for identifying hypersensitive phenotypes, rather than relying solely on absolute reflux burden[2,5].

Additionally, consistently low REs (<40) across all patients, coupled with preserved esophageal motility and intact mucosal integrity, distinguish this population from GERD and structural motility disorders. The diagnostic precision afforded by combined MII-pH monitoring, HREM, and detailed symptom profiling emphasizes the necessity of a multimodal approach in patients with esophageal symptoms without erosive disease[21,22,23].

Further, SI-positive patients exhibited elevated acid exposure and reflux parameters alongside reduced LES pressure, while SAP-positive patients, despite lower acid exposure and symptom indices, demonstrated increased esophageal contractility. MNBI values remained independent of SI or SAP status. Mean AET and DeMeester scores were within physiological ranges; nonetheless, a high proportion displayed positive SAP values, indicating temporal reflux–symptom associations despite normal acid burden. These findings are consistent with the Lyon Consensus 2.0, recognizing HE as a disorder of physiological reflux burden coupled with heightened sensory perception[5]. MII-pH confirmed reflux predominance in upright and postprandial periods, further supporting the functional symptom nature. An MNBI above 2500 Ω in most patients suggests a preserved mucosal barrier, effectively excluding chronic GERD[22,25].

IRP reflects the adequacy of LES relaxation during swallowing. Elevated IRP indicates impaired relaxation, which may result in esophageal outflow obstruction and contribute to symptom generation. In patients with HE, assessment of IRP provides valuable insight into the interplay between esophageal motility and symptom perception. HREM in our cohort demonstrated preserved peristalsis in the majority of patients, with LES resting pressure and IRP largely within normal limits, effectively excluding major esophageal motility disorders and reinforcing HE as predominantly a sensory functional disorder. The absence of significant motility abnormalities further strengthens diagnostic confidence and supports a therapeutic approach focused on neuromodulation rather than prokinetic agents[3,4,7–9]. Across various symptom subgroups—including heartburn, regurgitation, chest pain, and dysphagia—reflux and motility metrics showed minimal differences between symptom-positive and -negative patients, underscoring HE's complex pathophysiology and the role of visceral hypersensitivity[9,28]. Elevated LES resting pressure in chest pain patients may suggest hypercontractility or increased sphincter tone as a contributing factor.

MNBI, reflecting mucosal integrity, did not significantly vary across symptom groups, indicating mucosal injury is unlikely the symptom driver in HE. SI-positive patients showed significantly higher AET, DeMeester scores, and reflux frequency with concomitantly lower LES pressures facilitating reflux. Comparable MNBI between SI-positive and negative

groups suggests that transient REs in intact mucosa suffice to trigger symptoms in hypersensitive individuals.

Interestingly, SAP-positive patients exhibited lower acid exposure and SI scores compared to SAP-negative counterparts, challenging assumptions that SAP positivity equates to increased reflux burden[29-33]. The frequent discordance between SI and SAP—with most SAP-positive patients SI-negative and vice versa—highlights their distinct roles in symptom characterization, with SAP being less affected by symptom frequency fluctuations[29].

Finally, the high prevalence of SAP positivity despite normal acid exposure and DeMeester scores implies a significant role for non-acidic or weakly acidic reflux in symptom generation, consistent with Rome IV criteria for reflux hypersensitivity[6,9]. Collectively, these data advocate for diagnostic approaches extending beyond traditional reflux metrics, incorporating sensory testing and neuromodulatory mechanisms to better delineate functional phenotypes and tailor individualized therapy.

Therapeutic analysis revealed similar total reflux times and certain acid exposure parameters across treatment modalities; however, esophageal motility and reflux characteristics—particularly postprandial reflux and LES pressure—varied significantly by therapy type, influencing symptom perception and clinical outcomes. Notably, PPI monotherapy yielded limited efficacy, with only 37.3% of patients reporting improvement, consistent with existing evidence that acid suppression alone is often insufficient in functional esophageal disorders[9,27,28]. Conversely, second-line neuromodulator treatment—primarily selective SSRIs—achieved symptom relief in 98.9% of patients, supporting the concept that central neuromodulation via descending inhibitory pathways and altered esophageal sensory thresholds plays a pivotal role in managing functional esophageal pain, especially in individuals with visceral hypersensitivity and psychiatric comorbidities[8,9,26].

Emerging evidence endorses incorporating pre-treatment esophageal motility assessment to tailor therapy, particularly in optimizing neuromodulator use and reducing unnecessary acid suppression[10,34]. Nonetheless, motility patterns alone do not reliably predict treatment response. Instead, clinical improvement correlated more strongly with reductions in reflux burden and enhanced bolus clearance—especially in the supine position—highlighting the greater relevance of functional reflux metrics over isolated motility findings in determining therapeutic success in reflux hypersensitivity.

Our findings indicate that HE is primarily driven by altered sensory perception rather than structural abnormalities or acid exposure. The inconsistent correlation between symptoms and reflux or motility parameters suggests perceptual dysregulation, though these are preliminary conclusions. Diagnostic strategies should go beyond acid exposure and motility, incorporating symptom association indices like SI and SAP for improved clinical insight. MNBI, while not diagnostic alone, helps assess mucosal integrity. Neuromodulatory treatments—including tricyclic antidepressants, SSRIs, and behavioral therapies—are more effective than acid suppression in HE[7,8,9,26,27] emphasizing the need to address neurosensory dysfunction alongside physiological factors. Further prospective studies integrating MII-pH, HREM, and psychogastroenterological evaluations are needed. Research should validate biomarkers for esophageal hypersensitivity and investigate the role of elevated DCI or IRP in hypersensitive subgroups[32,33]. Randomized trials are crucial to assess neuromodulatory and behavioral treatment efficacy and to personalize therapy based on symptom-reflux associations.

This retrospective, single-center study has several limitations, including potential selection bias, lack of validated psychological assessments, small subgroup sizes, and the absence of direct testing for visceral hypersensitivity. Moreover, the generalizability of the findings may be restricted due to variability in clinical practice. The exceptionally high efficacy rate observed with SSRI therapy should also be interpreted cautiously within these methodological constraints. As a retrospective analysis, detailed data regarding the specific SSRI type, dosage, treatment duration beyond three months, and adverse effects could not be systematically retrieved. In addition, the high response rate may partially reflect careful patient selection and the inclusion of a homogeneous hypersensitive esophagus population diagnosed according to the Lyon Consensus 2.0 criteria. Future prospective, multicenter studies with comprehensive clinical and psychological assessments are warranted to validate and expand upon these findings. Another limitation of our study is that although the presence of *H. pylori* infection was detected in some patients, information regarding whether they received eradication therapy was not available. In addition, because of the small sample size, the potential influence of *H. Pylori* treatment on HE could not be adequately evaluated.

Strengths include a thorough multimodal diagnostic approach (MII-pH, HREM, SI, SAP) that captures HE heterogeneity beyond acid metrics. Real-world treatment data reveal a disconnect between objective findings and symptom relief. The inclusion of MNBI provides insight into mucosal integrity and sensory dysfunction. Overall, results support a neurosensory-centered model emphasizing personalized, symptom-focused care.

This study highlights HE as a distinct entity from classical GERD, characterized by normal acid

exposure, functional esophageal features, and poor symptom-physiology correlation. Traditional metrics like AET, DeMeester, and manometry inadequately reflect symptom burden, whereas combined use of SI, SAP, and MNBI offers better clinical insight. Treatment response was not tied to reflux or motility measures, underscoring the need for individualized, neurosensory-based approaches. Neuromodulators may be more effective than acid suppression, especially in patients with normal acid exposure but persistent symptoms. Improved reflux clearance and elevated DCI in SAP-positive patients suggest esophageal hypercontractility's role in symptom perception. Overall, the findings advocate for a neurosensory-focused diagnostic and therapeutic paradigm in HE, with future research needed to identify biomarkers and tailor treatments.

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