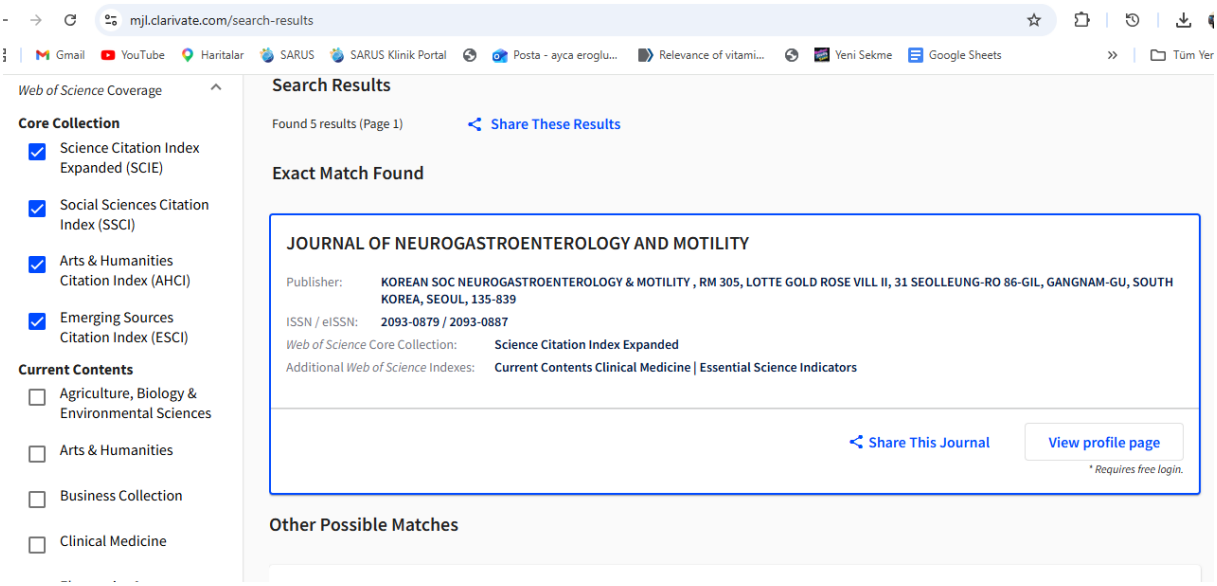

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Ineffective Esophageal Motility and Its Predictors in Gastroesophageal Reflux Disease Patients With Pathologic Acid Exposure Time

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Background/Aims: Although gastroesophageal reflux disease (GERD) and ineffective esophageal motility (IEM) often coexist, the directionality of their relationship remains uncertain. Clarifying physiological predictors of IEM in GERD patients with objectively verified pathological acid exposure may facilitate more personalized treatment strategies.

Methods: This retrospective analysis included 289 patients with typical reflux symptoms and abnormal acid exposure (acid exposure time > 6%) confirmed by 24-hour pH-impedance monitoring. Esophageal motility was assessed using high-resolution manometry, while mucosal integrity was evaluated through distal mean nocturnal baseline impedance (MNBI). Patients were categorized into normal motility and IEM groups. Clinical, endoscopic, manometric, and impedance parameters were compared between the groups.

Results: IEM was identified in 41.5% of patients. Compared with those showing normal motility, the IEM group was older (median 51.5 vs 44 years, $P < 0.001$), had reduced lower esophageal sphincter (LES) pressure (15 vs 19 mmHg, $P = 0.006$), and exhibited decreased distal MNBI (1300 vs 1780 Ω, $P = 0.005$). Multivariate regression revealed prolonged upright bolus exposure, reduced LES pressure, delayed supine distal latency, and MNBI < 1500 Ω as independent predictors of IEM. No significant associations were observed with diabetes or *Helicobacter pylori* infection.

Conclusions: In GERD patients with confirmed pathological acid exposure, IEM is common and associated with weakened LES pressure, delayed peristalsis, and reduced mucosal integrity. The link between low MNBI and IEM suggests an interaction between epithelial barrier dysfunction and esophageal motility, emphasizing the need for comprehensive functional evaluation in GERD management.

Keywords: Acid exposure; Esophageal motility disorders; Gastroesophageal reflux; Impedance; Manometry

INTRODUCTION

Gastroesophageal reflux disease (GERD) is a frequently encountered gastrointestinal condition characterized by the retrograde movement of stomach contents into the esophagus, most often manifesting as heartburn and regurgitation. Chronic exposure to refluxate may result in esophageal mucosal damage and complications, including erosive esophagitis and Barrett's esophagus. Acid exposure time (AET), measured during a 24-hour multichannel intraluminal impedance–pH (MII-pH) study, is a fundamental diagnostic parameter in GERD, representing the proportion of time the esophageal pH remains below 4. The Lyon Consensus 2.0 (2024) considers an AET exceeding 6% as definitive evidence of pathological acid reflux.[1]

Effective esophageal motility is essential for the proper clearance of refluxed gastric material. The Chicago classification version 4.0 (v4.0) characterizes ineffective esophageal motility (IEM) as the presence of over 70% ineffective swallows or a minimum of 50% failed swallows on high-resolution esophageal manometry (HREM), providing a uniform framework for assessing peristaltic function.[2] In addition to lower esophageal sphincter (LES) competence, coordinated esophageal motility and intact mucosal integrity are crucial for maintaining normal esophageal function.

Advances in impedance-based metrics, including mean nocturnal baseline impedance (MNBI) and the post-reflux swallow-induced peristaltic wave (PSPW) index, have contributed to a better understanding of GERD mechanisms.[3] MNBI provides a surrogate for esophageal mucosal integrity, whereas the PSPW index reflects the efficiency of refluxate clearance.[4] Despite their potential in classifying GERD phenotypes, the PSPW index was omitted from the 2024 Lyon Consensus 2.0 because of limited reproducibility and a lack of standardized methodology.[1]

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Although diagnostic technologies have advanced, the interplay between acid reflux and esophageal motility abnormalities remains incompletely defined. Chronic acid exposure is proposed to impair motility through inflammation-driven neuromuscular injury. Consistent with this, treatments such as anti-reflux mucosal ablation have demonstrated improvements in LES pressure and esophageal contractility along with reductions in acid exposure, suggesting that reflux-induced motility deficits may be partially reversible.[5] On the other hand, primary motility disorders, including IEM, can compromise clearance of refluxate and contribute to more severe GERD, indicating that motility dysfunction may both precede and amplify reflux pathology.[6-8]

Anatomical alterations at the esophagogastric junction (EGJ), particularly hiatal hernia (HH), may further influence the relationship between reflux and esophageal motility. Recent esophageal manometry studies have identified HH as an independent predictor of IEM, even among patients without elevated AET, suggesting that structural disruptions can directly compromise esophageal motor function.[6]

These observations highlight a potentially bidirectional and synergistic interaction between pathological acid exposure and esophageal motility dysfunction, although the underlying mechanisms remain unclear. The present study aims to identify clinical, endoscopic, manometric, and impedance-based predictors of IEM in patients with objectively confirmed pathological acid exposure (AET > 6%). By stratifying patients according to HREM findings and incorporating metrics such as MNBI, we seek to elucidate factors contributing to esophageal motility impairment within the GERD spectrum.

MATERIALS AND METHODS

Study Design and Population

This retrospective observational study was carried out at the Department of Gastroenterology Kocaeli University Faculty of Medicine, Kocaeli, Turkey, from January 2021 to January 2024. Adult patients with typical GERD symptoms persisting for at least 6 months who had undergone both HREM and MII-pH monitoring were considered for inclusion.

Approval for the study protocol was obtained from the Clinical Research Ethics Committee of Kocaeli University Faculty of Medicine (protocol no. 2025/149; dated 27 March 2025), and all procedures were performed in line with the Declaration of Helsinki and Good Clinical Practice standards. The requirement for written informed consent was waived by the institutional review board due to the retrospective nature of this study.

A total of 289 patients were included in the analysis. Participants were eligible for inclusion if they met the following criteria: (1) objectively confirmed pathological acid reflux, defined by an AET > 6% according to the Lyon Consensus 2.0;[1] (2) completion of both MII-pH and HREM studies; (3) availability of upper gastrointestinal endoscopy findings; and (4) completion of the GERD questionnaire.[9]

Exclusion criteria were as follows: achalasia (n = 6), EGJ outflow obstruction (n = 5), history of any malignancy (n = 4), MII-pH monitoring duration under 22 hours (n = 10), severe systemic illnesses such as chronic kidney disease, congestive heart failure, or cirrhosis (n = 10), prior upper gastrointestinal surgery (n = 7), and HH larger than 3 cm (n = 5). Following the application of these criteria, the final study cohort was analyzed for clinical, endoscopic, and functional parameters.

All patients underwent MII-pH and HREM after discontinuation of proton pump inhibitors (PPIs) and other acid-suppressive medications for at least 2 weeks, to ensure that measurements reflected the baseline esophageal physiology. Demographic information and symptom profiles were collected from medical records and standardized reflux questionnaires.[9] MII-pH data were analyzed following the Lyon Consensus 2.0, esophagitis severity was classified according to the Los Angeles (LA) grading system,[10] and esophageal motility disorders were defined based on the Chicago classification v4.0.[2]

Upper Gastrointestinal Endoscopy

All patients received upper gastrointestinal endoscopy due to the presence of reflux-related clinical symptoms. Procedures were performed using a FUJIFILM EG-760R gastroscope (FUJIFILM Corp, Tokyo, Japan). Endoscopic observations focused on HH, LES laxity, reflux esophagitis, and gastritis.

A hypotensive EGJ was defined as a gastroesophageal junction with a widely open or lax appearance, incomplete closure of the distal esophagus at rest, or absence of a prominent mucosal ridge. In addition, the gastroesophageal flap valve was evaluated in retroflexed view using Hill's classification (grades I-IV), which provides a standardized assessment of EGJ competence.[11] In grade I, the valve closely wraps around the endoscope, indicating normal function and effective closure; grade II demonstrates occasional opening with breathing, suggesting mild loosening; grade III shows a valve that remains largely open and does not fully close, reflecting significant dysfunction; and grade IV is characterized by the absence of a visible flap with a fully open junction, indicating severe impairment of the anti-reflux mechanism. Figure shows a representative image from a single patient demonstrating Hill grade 3. Since patients with hiatal hernias exceeding 3 cm were excluded

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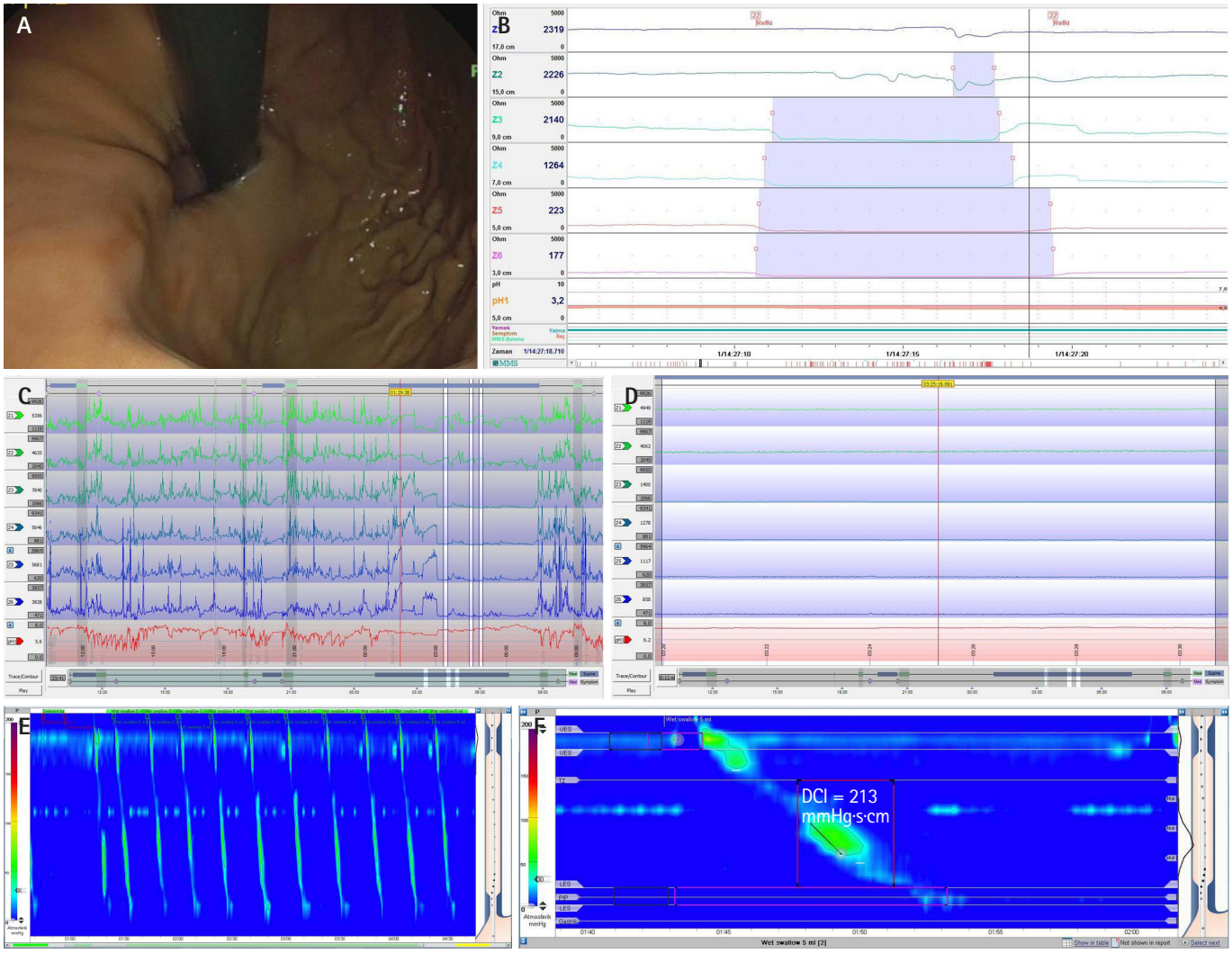


Figure. A representative case of pathological gastroesophageal reflux disease (GERD) associated with ineffective esophageal motility (IEM) is shown, integrating endoscopic, 24-hour multichannel intraluminal impedance–pH (MII-pH) monitoring, and high-resolution esophageal manometry (HREM) findings. Upper gastrointestinal endoscopy demonstrated a Hill grade 3 (A) gastroesophageal flap valve, which remained largely open and did not fully close, without evidence of erosive esophagitis. MII-pH monitoring (B) revealed pathological acid reflux, with an acid exposure time (AET) of 11.6% and 43 reflux episodes, exceeding the pathological threshold of 6%. Symptom–reflux association was significant, with a symptom index of 66.6% and a symptom association probability of 87.8%. For mean nocturnal baseline impedance (MNBI) assessment, a stable artifact-free nocturnal tracing (C) was selected, and three measurements between 1 AM and 3 AM (D) were averaged, yielding an MNBI of approximately 1274 Ω at the Z5 channel. HREM (E) demonstrated IEM according to Chicago classification version 4.0, with 10% intact, 60% weak (distal contractile integral [DCI], 100–450 mmHg·s·cm) (F), and 30% failed (DCI < 100 mmHg·s·cm) peristaltic contractions. IEM is defined by > 70% ineffective (weak) or ≥ 50% failed swallows, indicating impaired esophageal clearance and bolus transit. The average of 10 wet swallows showed a lower esophageal sphincter (LES) resting pressure of 11 mmHg, consistent with hypotension, an integrated relaxation pressure (IRP) of 9 mmHg, and a DCI of 213 mmHg·s·cm, indicative of weak peristaltic contractions, while contractile front velocity (CFV, 4.6 cm/sec) and distal latency (DL, 6 seconds) were within normal limits, suggesting impaired esophageal clearance despite preserved peristaltic timing and propagation.

from the study, cases corresponding to Hill grade IV, which reflect a completely absent gastroesophageal flap valve, were not included in the analyzed cohort.

pH–Impedance Monitoring

MII-pH monitoring was performed using a single-use Digitrapper VersaFlex-Z catheter (Medtronic, Minneapolis, MN, USA). Patients discontinued PPIs at least 2 weeks prior to the procedure and fasted for a minimum of six hours before catheter placement. The pH sensor was placed 5 cm above the LES, based on measurements from preceding high-resolution esophageal manometry. To reduce measurement variability, MNBI values were manually assessed by a single experienced physician. Automated analysis was performed using Digitrapper Reflux Reader software v6.1 (Medtron-

ic), followed by manual verification. During monitoring, patients maintained their usual daily routines and recorded meals, symptoms, and posture changes in a standardized diary.

The percentage of time that esophageal pH remained below 4.0 over a 24-hour period was used to calculate AET. An AET exceeding 6% was regarded as pathological according to the Lyon Consensus 2.0.[1]

High-resolution Esophageal Manometry

HREM was performed using a multichannel water-perfused system (MMS; Medical Measurement Systems BV, Enschede, The Netherlands, now part of Laborie Medical Technologies), integrated with Polygram Net software (version 4.01). Studies were conducted in both supine and upright positions, and data were interpreted per the Chicago classification v4.0.[2] Integrated relaxation pressure (IRP): defined as the average of the lowest 4 seconds of pressure values within the 10-second post-swallow period; it assesses lower esophageal sphincter relaxation. LES resting pressure: reflects basal tone of the LES.

Distal contractile integral (DCI) is a composite metric that quantifies the amplitude, duration, and length of esophageal contractions (expressed in mmHg·s·cm). A DCI value below 450 mmHg·s·cm is indicative of weak peristalsis, whereas a value less than 100 mmHg·s·cm denotes failed peristalsis.

Contractile front velocity: speed of peristaltic wave propagation along the esophagus. The peristaltic break length represents the extent of interruption in the 20 mmHg isobaric contour; breaks longer than 5 cm are associated with reduced efficacy of esophageal bolus clearance. DL represents the time elapsed from the onset of a swallow to the contractile deceleration point. A DL shorter than 4.5 seconds may indicate the presence of spastic esophageal contractions. Particular emphasis was placed on diagnosing IEM, defined as > 70% ineffective swallows (DCI < 450 mmHg·s·cm) or ≥ 50% failed swallows, in the absence of EGJ outflow obstruction.[2]

Data Stratification and Grouping

Only patients with pathological acid exposure (AET > 6%) were included, while those with AET ≤ 6% were excluded to ensure diagnostic consistency. The final cohort was stratified based on HREM findings into 2 groups: individuals with normal esophageal motility and those with IEM according to the Chicago classification v4.0.[2] Comparative analyses encompassed a range of variables, including demographic characteristics (age, sex, body mass index [BMI]), lifestyle factors (tobacco and alcohol use), comorbidities (hypertension, diabetes mellitus [DM]), endoscopic findings (LA classification, presence of HH, *Helicobacter pylori* infection), symptom profiles (frequency and severity of typical and atypical GERD symptoms), and MII-pH parameters (total AET, number of reflux episodes, symptom index, symptom association probability, and MNBI). Distal MNBI was determined manually, rather than through an automated system, at 3 esophageal levels (Z1, Z2, and Z5) using overnight MII-pH recordings. At each level, 3 separate 10-minute nocturnal periods—around 1 AM, 2 AM, and 3 AM—were chosen during times without swallows, reflux events, or technical artifacts. The same observer reviewed all measurements, and the mean of the three intervals at each level was calculated to provide a consistent estimate of esophageal mucosal integrity while reducing variability related to the observer.

Statistical Methods

Statistical analyses were performed using IBM SPSS Statistics version 29.0 (IBM Corp, Armonk, NY, USA). The distribution of continuous variables was examined using the Kolmogorov–Smirnov and Shapiro–Wilk tests. Normally distributed data are expressed as mean ± standard deviation, and non-normally distributed variables are summarized as median and interquartile range.

Categorical variables were summarized as frequencies and percentages. Comparisons of continuous variables between groups were performed using the Kruskal–Wallis test, followed by Dunn's post hoc analysis for pairwise comparisons when applicable. Associations between categorical variables were evaluated using the chi-square test, and Bonferroni correction was applied to adjust for multiple testing.

A two-tailed P-value of < 0.05 was considered statistically significant. Variables demonstrating significance in univariate analysis ($P < 0.05$) were subsequently entered into a multivariate logistic regression model to identify independent predictors of IEM. Adjusted odds ratios (ORs) and corresponding 95% confidence intervals (CIs) were calculated for all variables retained in the final model.

Data Availability Statement

The data presented in this study are available on request from the corresponding author.

RESULTS

The final analysis comprised 289 patients who demonstrated objectively confirmed pathological acid exposure, defined as an AET greater than 6%. The cohort consisted predominantly of male participants (60.6%, n = 175), while females comprised 39.4% (n = 114). The median age was 47 (37-57) years, and the median BMI was 26.8 (24.49-29.60) kg/m^2.

According to BMI classification, 1.0% (n = 3) were underweight

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(BMI ≤ 18.5), 27.0% (n = 78) had normal weight (18.5-24.9), 49.5% (n = 143) were overweight (25-29.9), and 22.5% (n = 65) were obese (≥ 30). These data reflect a relatively young and predominantly overweight population, consistent with typical GERD demographics.

Comorbidities and Lifestyle Factors

At least 1 comorbidity was present in 45.5% (n = 131) of patients. The most frequent conditions included hypertension (22.8%, n = 66), type 2 DM (12.5%, n = 36), allergies (9.7%), coronary artery disease (8.3%, n = 24), cardiac arrhythmia (8.3%, n = 24), asthma or chronic bronchitis (7.3%), rheumatologic disorders (6.2%, n = 18), and hyperlipidemia (4.5%, n = 13). The median comorbidity duration was 60 (24-120) months.

Among the 36 patients with type 2 DM, the median HbA1c was 6.6 (6.2-7.0). HREM revealed normal motility in 14 and IEM in 22 diabetic patients. The difference in HbA1c between these subgroups was not statistically significant (P = 0.619). Only 2 patients exhibited microvascular complications.

Regarding lifestyle habits, 55.4% (n = 160) were non-smokers, 26.0% (n = 75) were current smokers, and 18.7% (n = 54) were former smokers. Among participants who smoked or had previously smoked, the median age at initiation was 19 years (15-20), and the median cumulative smoking exposure reached 28 pack-years (8.5-42). Patients with IEM had a significantly longer duration since smoking cessation, suggesting a potential residual effect of prior tobacco exposure on esophageal motility. Alcohol consumption was reported by 10% of the cohort, with most drinking 1-2 times per week.

Symptom Profiles

Regurgitation (83%) and heartburn (73%) were the most commonly reported symptoms. Symptom duration varied widely, with a median of 36 (12-84) months. Dysphagia was reported in 42.6% (n = 72) of patients with normal motility and 33.3% (n = 40) of those with IEM, while its absence was more common in the IEM group (66.7% vs 57.4%). However, this difference did not reach statistical significance (P = 0.111).

Patients with normal motility reported significantly longer durations of regurgitation (36 [12-72] vs 24 [12-60] months, P = 0.034) and dysphagia (24 [12-36] vs 12 [9.3-57] months, P = 0.037) compared to those with IEM. These observations imply that the persistence of symptoms does not consistently correlate with the presence of esophageal motility disorders.

Helicobacter pylori Status

H. pylori status was determined by gastric biopsy. The bacterium was identified in the antrum of 28.7% (n = 83) and in the corpus of 15.6% (n = 45) of patients.

Biopsy data were unavailable in 14.2% (n = 41) of antral samples and 16.3% (n = 47) of corpus samples. Overall, 28.7% (n = 83) tested positive for *H. pylori*, 57.1% (n = 165) were negative, and 14.2% had insufficient data. No statistically significant association was found between *H. pylori* status and esophageal motility patterns (P = 0.274), suggesting limited involvement of *H. pylori* in the pathophysiology of IEM.

Endoscopic Findings

Endoscopically, EGJ appeared normal in 51.2 % (n = 148) of patients, whereas a hypotensive morphology was observed in 48.8% (n = 141). A small HH (< 3 cm) was identified in 28.4% (n = 82).

Among patients with normal manometry, 50.9% (n = 86) exhibited a normal EGJ appearance, whereas 49.1% (n = 83) demonstrated a hypotensive EGJ. In the IEM group, 51.7% (n = 62) had a normal EGJ appearance, and 48.3% (n = 58) presented with a hypotensive EGJ (P = 0.896). In the IEM group, 70.8% (n = 85) had no HH, and 29.2% (n = 35) had HH, with no significant association between manometry status and the presence of HH (P = 0.801). Concerning endoscopic valve competence, 50.3% (n = 85) of patients with normal manometry were classified as Hill grade I, 22.5% (n = 38) as grade II, and 27.2% (n = 46) as grade III. In the IEM group, 51.7% (n = 62) were Hill grade I, 20.0% (n = 24) grade II, and 28.3% (n = 34) grade III, with no significant relationship observed between manometry status and Hill grade (P = 0.878).

According to the LA classification, 76.5% (n = 221) showed no visible esophagitis. LA Grade A was observed in 14.5% (n = 42), and Grades B to D in 9.0% (n = 26). These observations demonstrate that substantial acid exposure may be present without endoscopic evidence of mucosal breaks, supporting the paradigm of non-erosive reflux disease.

pH-Impedance Findings

All patients had objectively confirmed GERD, defined by AET > 6% on MII-pH monitoring. The median upright AET was 12 (8.6-17.8), and the median DeMeester score was 37.7 (28.6-58.7), indicating substantial acid exposure across the cohort. The median number of reflux episodes was 44 (28.5-62.0).

Mucosal Integrity Values

MNBI, serving as an indicator of esophageal mucosal integrity, demonstrated median values of 1650 Ω (1033-2258) at the distal esophagus (Z5) and 2900 Ω (2046-3600) and 3042 Ω (2230-3808) at the proximal esophagus (Z2 and Z1, respectively). These values indicate varying degrees of mucosal compromise, with the most

pronounced reduction observed in the distal esophagus (Z5), consistent with chronic acid injury. The baseline demographic and clinical features of the study cohort are presented in Table 1.

Comparison of Ineffective Esophageal Motility and Normal Motility Groups

Based on HREM findings, participants were categorized into normal motility (n = 169) and IEM (n = 120) groups. IEM was observed in 41.5% of patients, indicating that esophageal motor impairment is common even in the context of uniformly pathological acid exposure (AET > 6%).

Table 1. Baseline Characteristics and Clinical Features of the Study Cohort

Variable	Value
Male	175 (60.6)
Female	114 (39.4)
Age (yr)	47.0 (37.0-57.0)
BMI (kg/m²)[a]	26.8 (24.5-29.6)
Comorbidities	131 (45.5)
Non-smokers	160 (55.4)
Current smokers	75 (26.0)
Former smokers	54 (18.7)
Alcohol consumption	29 (10.0)
Most common symptoms	
Regurgitation	240 (83.0)
Heartburn	211 (73.0)
Normal GEJ	162 (56.1)
Hypotensive GEJ	125 (43.2)
Hiatal hernia (< 3 cm)	83 (28.7)
Normal esophagus	221 (76.5)
LA-A esophagitis	42 (14.5)
LA-B or D esophagitis	26 (9.0)
AET	12.0 (8.6-17.8)
Reflux episodes	44.0 (28.5-62.0)
DeMeester score	37.7 (28.6-58.7)
Symptom-reflux association	164 (56.8)
MNBI-Z1 (Ω)	3042 (2230-3809)
MNBI-Z2 (Ω)	2900 (2046-3600)
MNBI-Z5 (Ω)	1650 (1033-2258)

[a]Body mass index (BMI) classification: underweight (≤ 18.5 kg/m²), normal weight (18.5-24.9 kg/m²), overweight (25.0-29.9 kg/m²), and obese (≥ 30.0 kg/m²). Symptom-Reflux Association: Indicates a positive correlation between symptoms and reflux events based on a positive symptom index (≥ 50%) and/or symptom association probability (≥ 95%).
IQR, interquartile range; GEJ, gastroesophageal junction; LA, Los Angeles classification; AET, acid exposure time; MNBI, mean nocturnal baseline impedance; Z1-Z5, impedance measurement channels (proximal to distal).
Values are presented as number (%) for categorical variables and median (interquartile range) for continuous variables unless otherwise specified.

Demographic and anthropometric comparisons

Sex distribution showed 39.4% females and 60.6% males overall; males were more frequent in the IEM group (65.8%) than normal motility (43.2%) but without statistical significance (P = 0.143); median age was significantly higher in the IEM group at 51.5 years (40-62) compared to 44 years (36-55) in the normal motility group (P < 0.001), while BMI was similar between groups: 26.9 (24.3-29.0) kg/m² for normal motility and 26.6 (23.8-29.0) kg/m² for IEM (P = 0.319).

Comorbidities and diabetes mellitus

Among patients without comorbidities, 63.9% had normal motility and 36.1% had IEM, whereas among those with comorbidities, 51.9% had normal motility and 48.1% had IEM (P = 0.042), suggesting systemic comorbidities may predispose to esophageal motor dysfunction; diabetes prevalence was significantly higher in the IEM group (18.3%) compared to normal motility (8.3%) (P = 0.011), with 61.1% of diabetics exhibiting IEM versus 38.9% with normal motility.

Symptom profiles

Heartburn occurred at similar rates in both groups (P = 0.894). While the median duration of symptoms tended to be longer in the IEM cohort [36 (18-60) months] compared with the normal motility group [24 (12-36) months], the difference did not reach statistical significance (P = 0.359). Severity scores were comparable, but the frequency of heartburn episodes was elevated in the IEM group (P = 0.009). Dysphagia prevalence was also similar (P = 0.114), with 64.3% of dysphagic patients showing normal motility and 35.7% IEM, though dysphagia episodes were shorter and less frequent in the IEM group (P = 0.037 and P = 0.013). Regurgitation, reported by 83% overall, was more frequent in normal motility patients (87.0%) versus IEM (77.5%), with a significantly longer median duration in the IEM group [36 (12-60) months vs 24 (12-36) months; P = 0.034]; frequency and severity were higher in the normal motility group (P = 0.020 and P = 0.018). Other GI symptoms like epigastric pain (63.3% vs 34.8%, P = 0.007) and frequent belching (52.7% vs 40.0%, P = 0.034) were more common in normal motility patients, while retrosternal pain showed no significant difference (P = 0.278). Symptom–reflux association, based on symptom index or symptom association probability, was positive in 56.8% of patients, with no significant difference between normal motility (58.0%) and IEM (55.1%) groups (P = 0.818 and P = 0.915), suggesting that symptom frequency or severity does not reliably reflect esophageal motility abnormalities.

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pH–Impedance and bolus exposure metrics

The median DeMeester score was 39.6 (33.5-58.3) in the IEM group and 31.0 (24.0-46.0) in the normal motility group, though this difference was not statistically significant ($P = 0.209$); upright AET was higher in the IEM group [15.3% (11.0-28.0) vs 13.1% (8.3-19.0); $P = 0.098$], while supine AET was similar between groups [7.4% (4.4-13.6) vs 6.1% (3.9-9.0); $P = 0.915$]; upright bolus exposure time was significantly prolonged in the IEM group [1.5% (0.7-2.5)] compared to the normal motility group [1.2% (0.6-1.8); $P = 0.024$], whereas supine bolus exposure time was minimal and similar between groups [0.1% (0.0-0.4); $P = 0.624$].

Mucosal integrity

MNBI values measured at three esophageal levels showed Z1 (proximal-most) at 3017 (2200-3766) Ω in normal motility vs 3117 (2300-3850) Ω in IEM ($P = 0.680$) and Z2 (proximal) at 2929 (2050-3600) Ω in normal motility vs 2833 (2046–3617) Ω in IEM ($P = 0.497$), indicating preserved proximal mucosal integrity regardless of motility status; however, Z5 (distal) was significantly lower in the IEM group at 1300 (850-2122) Ω compared to 1780 (1140-2315) Ω in the normal motility group ($P = 0.005$), reflecting compromised distal mucosal integrity; threshold analysis revealed values below 1500 Ω were significantly more common in the IEM group ($P = 0.006$), with stratification by MNBI categories (< 1500, 1500-2500, > 2500 Ω) showing patients with MNBI < 1500 Ω were more likely to have IEM, confirmed by pairwise post hoc Bonferroni comparisons ($P = 0.006$), and a linear-by-linear association test suggested a trend toward decreasing MNBI with worsening motility ($P = 0.060$). Collectively, these findings support the notion that distal mucosal impairment (low MNBI) is tightly linked to IEM, while proximal mucosal integrity remains relatively unaffected. Table 2 summarizes the comparison of demographic, clinical, and physiological characteristics between the normal esophageal motility and IEM groups.

Independent predictors and manometric characteristics of ineffective esophageal motility

When HREM metrics were compared, patients with IEM exhibited a lower median LES pressure (15 mmHg [9-21]) than those with normal motility (19 mmHg [12-25]; P = 0.006), reflecting compromised sphincter function potentially predisposing to increased reflux.

The median DL was 7.0 seconds in both the IEM and normal groups; however, the IEM group exhibited a significantly wider and slightly prolonged DL distribution (6.65-8.0 vs 6.1-7.9; $P = 0.021$), indicating subtle neuromuscular delay. In contrast, IRP, a marker of EGJ relaxation, did not differ significantly between groups (normal: 7 mmHg [4-12]; IEM: 6 mmHg [2.3-10.0], $P = 0.162$), indicating preserved LES relaxation in both cohorts.

In univariate analysis, several variables were significantly associated with IEM. While DM increased the odds of IEM (OR: 2.49, 95% CI: 1.21-5.08; $P = 0.013$), this effect did not remain significant after multivariate adjustment ($P = 0.126$), indicating possible confounding. Independent predictors in the multivariate model included current smoking (OR: 0.39, 95% CI: 0.18-0.83; $P = 0.016$), distal MNBI < 1500 Ω (OR: 0.50, 95% CI: 0.26-0.96; $P = 0.039$), increased upright bolus exposure (OR: 1.33, 95% CI: 1.06-1.66;

Table 2. Comparison of Demographic, Clinical, and Physiological Features Between Normal Esophageal Motility and Ineffective Esophageal Motility Groups

Parameter	Normal motility (n = 169)	IEM (n = 120)	*P*-value
Female	73 (43.2)	41 (34.2)	0.143
Male	96 (56.8)	79 (65.8)	
Age (yr)	44 (36.0-55.0)	51.5 (40.0-62.0)	< 0.001
BMI (kg/m^2)	26.9 (24.3-29.0)	26.6 (23.8-29.0)	0.319
Comorbidity	68 (51.9)	63 (48.1)	0.042
Type 2 DM	14 (8.3)	22 (18.3)	0.011
Heartburn	124 (73.4)	87 (72.5)	0.894
Regurgitation	147 (87.0)	93 (77.5)	0.050
Epigastric pain	107 (63.3)	57 (34.8)	0.007
Belching	89 (52.7)	48 (40.0)	0.034
Dysphagia	72 (42.6)	40 (33.3)	0.114
Upright AET (%)	13.1 (8.3-19.0)	15.3 (11.0-28.0)	0.098
Supine AET (%)	6.1 (3.9-9.0)	7.4 (4.4-13.6)	0.915
RE	31 (19.0-46.0)	34 (18.0-50.0)	0.865
Upright BET (%)	1.2 (0.6-1.8)	1.5 (0.7-2.5)	0.024
Supine BET (%)	0.1 (0.0-0.4)	0.1 (0.0-0.4)	0.624
SI	43 (0.0-68.0)	46 (0.0-75.0)	0.818
SAP	88 (0.0-100.0)	85 (0.0-100.0)	0.951
MNBI-Z1 (Ω)	3017 (2200-3766)	3117 (2300-3850)	0.680
MNBI-Z2 (Ω)	2929 (2050-3600)	2833 (2046-3617)	0.497
MNBI-Z5 (Ω)	1780 (1140-2315)	1300 (850-2122)	0.005
MNBI < 1500 Ω	63 (37.3)	67 (55.8)	0.006
MNBI 1500-2500 Ω	77 (45.6)	36 (30.0)	0.006
MNBI > 2500 Ω	29 (17.2)	17 (14.2)	0.130

IEM, Ineffective esophageal motility; BMI, body mass index; DM, diabetes mellitus; AET, acid exposure time; RE, reflux episodes; BET, bolus exposure time; SI, symptom index; SAP, symptom association probability; MNBI, mean nocturnal baseline impedance; Z1-Z5, impedance measurement channels (proximal to distal).
Values are presented as number (%) for categorical variables and median (interquartile range) for continuous variables unless otherwise specified.
A *P*-value of < 0.05 was considered statistically significant.

Table 3. Univariate and Multivariate Logistic Regression Analysis of Factors Associated With Ineffective Esophageal Motility

Variable	Univariate OR (95% CI)	Univariate *P*	Multivariate OR (95% CI)	Multivariate *P*
Age (yr)	1.04 (1.02-1.06)	0.001	1.02 (0.99-1.05)	0.076
Type 2 DM	2.49 (1.21-5.08)	0.013	2.14 (0.81-5.58)	0.126
Heartburn (once/wk)	1.52 (0.80-2.88)	0.200	1.61 (0.71-3.63)	0.251
Heartburn (2-3 times/week)	1.00 (0.53-1.88)	> 0.999	1.08 (0.49-2.41)	0.849
Heartburn (≥ 4 times/week)	0.47 (0.22-0.97)	0.042	0.87 (0.34-2.23)	0.765
Regurgitation (once/week)	0.54 (0.27-1.09)	0.870	0.61 (0.26-1.41)	0.246
Regurgitation (2-3 times/week)	0.68 (0.34-1.36)	0.272	0.73 (0.30-1.77)	0.489
Regurgitation (≥ 4 times/week)	0.26 (0.12-0.55)	0.001	0.49 (0.19-1.28)	0.147
Dysphagia (once/week)	1.09 (0.61-1.98)	0.763	1.82 (0.51-2.31)	0.149
Dysphagia (2-3 times/week)	0.53 (0.21-1.35)	0.184	0.61 (0.18-2.05)	0.424
Dysphagia (≥ 4 times/week)	0.24 (0.09-0.66)	0.006	0.41 (0.12-1.36)	0.149
Epigastric pain	0.52 (0.33-0.84)	0.008	0.73 (0.39-1.34)	0.307
Current smoker	0.41 (0.23-0.74)	0.003	0.39 (0.18-0.83)	0.016
Former smoker	0.67 (0.36-1.26)	0.210	0.44 (0.20-0.97)	0.041
BET (upright, %)	1.29 (1.08-1.54)	0.004	1.33 (1.06-1.66)	0.015
LES pressure (mmHg)	0.96 (0.93-0.99)	0.005	0.94 (0.91-0.98)	0.002
DL (supine, sec)	1.42 (1.13-1.80)	0.003	1.61 (1.21-2.15)	0.001
MNBI < 1500	0.44 (0.26-0.74)	0.002	0.50 (0.26-0.96)	0.039
MNBI 1500-2500	0.55 (0.28-1.10)	0.091	0.98 (0.41-2.33)	0.959

DM, diabetes mellitus; OR, odds ratio; CI, confidence interval; BET, bolus exposure time; LES, lower esophageal sphincter; DL, distal latency; MNBI, mean nocturnal baseline impedance.
This table summarizes independent risk factors for ineffective esophageal motility (IEM) identified via univariate and multivariate logistic regression analyses. Significant predictors of IEM in univariate analysis included diabetes mellitus, current smoking, reduced MNBI (< 1500 Ω), increased upright bolus exposure time, decreased LES pressure, and prolonged supine DL. In multivariate analysis, current smoking, reduced MNBI, increased upright bolus exposure time, decreased LES pressure, and prolonged supine distal latency remained independently associated with IEM. DM lost statistical significance after adjustment.

P = 0.015), decreased LES pressure (OR: 0.94, 95% CI: 0.91-0.98; *P* = 0.002), and prolonged supine distal latency (OR: 1.61, 95% CI: 1.21-2.15; *P* = 0.001). The model demonstrated good overall fit, as indicated by a statistically significant intercept (*P* < 0.001). Additionally, neither age (*P* = 0.076) nor symptom frequency—including heartburn, regurgitation, dysphagia, belching, and epigastric pain—independently predicted IEM after adjusting for covariates (Table 3). Collectively, these findings define a distinct GERD patient phenotype characterized by diminished LES tone, impaired bolus clearance, prolonged DL in the supine position, and compromised distal mucosal integrity—physiological features independently associated with IEM.

A representative patient with IEM is presented in Figure, illustrating endoscopic evaluation, HREM metrics, and MII-pH results, thereby exemplifying the physiologic interplay between IEM, impaired bolus clearance, and reflux burden.

DISCUSSION

In this well-characterized cohort of GERD patients with objectively confirmed pathological acid exposure, IEM was highly prevalent, observed in more than 40% of cases, highlighting its clinical significance. Despite comparable reflux burden, patients exhibited substantial heterogeneity in esophageal motor function and impedance-derived metrics, indicating that motor impairment contributes to GERD pathophysiology independently of acid exposure. The association of IEM with reduced LES pressure, prolonged upright bolus exposure, and decreased distal MNBI underscores the combined effect of impaired clearance and compromised mucosal integrity, supporting the concept that esophageal dysmotility represents an independent and clinically relevant pathophysiological axis in GERD rather than a simple epiphenomenon of reflux severity.

Age-related declines in esophageal neuromuscular function, including reduced peristaltic vigor and impaired secondary peristalsis, likely contribute to the increasing prevalence of IEM among

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older GERD patients.[12-20] Interestingly, symptom perception did not consistently correlate with motility impairment in our cohort: patients with preserved peristalsis often reported more prolonged regurgitation and dysphagia than those with IEM.[18,21-30] This dissociation underscores the role of altered visceral sensitivity and central sensory processing in modulating reflux symptoms independently of esophageal motor function.[19,21,22,24] Consequently, reliance on symptom burden alone may underestimate underlying motility abnormalities, highlighting the need for objective assessment using HREM and MII-pH monitoring across age groups.

Metabolic and lifestyle factors further influence esophageal motility. While obesity can increase reflux burden and mucosal injury, moderate obesity may preserve contractility, whereas morbid obesity (BMI ≥ 40) is linked to higher IEM prevalence, EGJ outflow obstruction, and elevated IRP.[31-38] In our cohort, BMI did not differ between patients with and without IEM, suggesting that motility impairment can occur independently of overall obesity. However, visceral adiposity, as assessed by waist circumference, is associated with increased GERD and mucosal compromise,[39] highlighting the importance of central adiposity in esophageal pathophysiology. Type 2 DM was linked to IEM in univariate analysis, though its effect was not independent in multivariate models, suggesting indirect mechanisms such as autonomic neuropathy or delayed gastric emptying.[40,41]

Smoking and alcohol intake can impair esophageal motility: nicotine reduces LES tone, slows clearance, and increases transient LES relaxations, whereas chronic alcohol intake can impair peristalsis and LES competence.[42-45] The inverse association between current smoking and IEM in our study may reflect residual confounding, reverse causality, or symptom-driven smoking cessation, and should not be interpreted as protective.

Structural factors, such as LES–crural diaphragm separation observed in HH, are known to correlate with increased reflux burden and abnormal MII-pH metrics.[46,47] Although HH has been linked to IEM, this relationship may be influenced by age and esophageal inflammation.[6,46] In our cohort, no significant associations were observed between esophageal motor patterns and endoscopic findings, including HH and esophagitis grade, possibly due to exclusion of patients with large HH (> 3 cm), suggesting that structural abnormalities alone are insufficient to predict motility dysfunction.

IEM was observed across the spectrum of GERD, affecting both erosive and non-erosive disease, yet its presence did not directly reflect disease severity.[47,48] Functionally, IEM impairs effective peristalsis and salivary-mediated clearance, prolonging esophageal acid contact and sustaining symptoms, particularly in patients with objectively documented pathological acid exposure.[47,49,50] In our cohort, IEM was independently associated with prolonged upright bolus exposure and reduced LES pressure, irrespective of reflux frequency or symptom correlation, suggesting clearance dysfunction that may occur independently of reflux events.[22,51-53] Endoscopic findings, including esophagitis, were similar between groups, indicating that mucosal injury primarily reflects acid exposure rather than motility impairment.[50]

The coexistence of IEM and reduced distal MNBI defines a distinct GERD phenotype characterized by impaired clearance and regionally concentrated mucosal vulnerability.[54-59] Prolonged distal latency in the supine position further supports delayed peristaltic propagation as a contributor to sustained reflux.[54,57,60]

In multivariate analysis, independent predictors of IEM included low distal MNBI (< 1500 Ω), reduced LES pressure, prolonged distal latency in the supine position, and increased upright bolus exposure, whereas neither age nor symptom burden independently predicted motility impairment. These findings reinforce the limitations of symptom-based assessment and underscore the importance of advanced physiological testing, including HREM and MII-pH monitoring, for accurate GERD phenotyping and individualized management.[61]

Clinical Implications

Our findings emphasize the critical importance of assessing esophageal motility in the diagnosis and management of GERD. The high prevalence of IEM, even in patients without severe esophagitis, highlights the limitations of relying solely on endoscopy or symptom-based evaluation. IEM may contribute to impaired bolus clearance, persistent reflux, and reduced response to PPIs. Incorporating HREM and MII-pH monitoring allows early identification of affected patients, facilitating individualized and targeted treatment planning.

Functional metrics such as distal MNBI, upright bolus exposure, and peristaltic integrity provide valuable guidance for precision-based management. The observed associations of IEM with aging, reduced LES pressure, and distal mucosal compromise underscore the importance of early detection for effective risk stratification and preoperative evaluation.

Limitations

This retrospective, single-center study design limits the generalizability of the findings and may overrepresent patients with more severe GERD. The cross-sectional nature of the study prevents causal inference, and manual interpretation of MNBI may be subject to observer variability. Additional unmeasured factors, including diet, sleep patterns, and anthropometric measures (such as abdominal and hip circumference), could have influenced the results and limit the assessment of central obesity's specific ef-

fects on esophageal motility and mucosal integrity. Furthermore, sensory testing and systematic analyses of reflux–symptom associations were not consistently available, which restricts insights into symptom perception and pathophysiological correlations.

Strengths

Despite these limitations, the study has several strengths. Strict inclusion criteria according to the Lyon Consensus 2.0 ensured a well-defined GERD cohort with pathological acid exposure (AET > 6%). Combined endoscopy, HREM, MII-pH, and impedance-derived MNBI allowed for a comprehensive assessment of esophageal motility and mucosal integrity. Conducted at a tertiary center, this cohort represents a clinically diverse, real-world population, thereby enhancing the external validity of the findings. Stratification by IEM status and multivariate analysis enabled identification of independent predictors while controlling for confounders such as age, LES pressure, MNBI, and bolus clearance. The study also examined the impact of metabolic comorbidities, including type 2 DM and obesity, on esophageal motility, further contributing to the understanding of GERD pathophysiology. Notably, many IEM patients did not exhibit endoscopic injury, highlighting the importance of functional testing for precise phenotyping.

In conclusion, IEM was frequently observed in GERD patients with pathological acid exposure and was independently associated with reduced LES pressure, impaired bolus clearance, and lower distal MNBI. Symptom severity and endoscopic findings did not consistently correspond to manometric abnormalities, underscoring the multifactorial nature of GERD. The reduction of distal MNBI in patients with IEM reflects regionally concentrated mucosal vulnerability and compromised epithelial integrity. These findings emphasize the importance of comprehensive physiological assessment using HREM and impedance measurements for accurate diagnosis and individualized management, particularly in patients with persistent or unexplained reflux. Future prospective studies are needed to elucidate the causal relationships between reflux burden and motor dysfunction and to determine whether therapies aimed at restoring motility can improve clinical outcomes and mucosal integrity.

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Conflicts of interest

None.

Author contributions

Conceptualization, methodology, validation, investigation, resources, writing—review and editing, supervision, and project administration: Ayça Eroğlu Haktanır and Altay Çelebi; software, data curation, writing—original draft preparation: Ayça Eroğlu Haktanır; formal analysis: Ayça Eroğlu Haktanır and Altay Çelebi; and All authors have read and agreed to the published version of the manuscript.

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