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Original Article

Validation of Lyon 2.0 Gastroesophageal Reflux Disease Consensus: Limited Clinical Utility of Mean Nocturnal Basal Impedance in Koreans

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Background/Aims
The Lyon Consensus 2.0 (Lyon 2.0) revised gastroesophageal reflux disease (GERD) definitions, incorporating Los Angeles (LA) grade B as diagnostic and mean nocturnal basal impedance (MNBI) as supplementary evidence. Asian populations show differing impedance-pH thresholds, with lower acid exposure time (AET) and higher MNBI values. The clinical validity of MNBI in Asian GERD patients remains uncertain. This study evaluated Lyon 2.0's applicability to Korean patients.

Methods
From January 2021 to August 2023, GERD-suspected patients underwent endoscopy, manometry, and pH testing. MNBI was measured 5 cm above the lower esophageal sphincter. Patients with major motor disorders, organic diseases, or prior foregut surgery were excluded. GERD was defined by AET ≥ 4% or LA grades B-D; non-GERD by AET < 4%, LA grade A or normal Z line with < 40 reflux episodes/day. The optimal MNBI threshold was determined via receiver operating characteristic curve analysis.

Results
Among 427 patients (mean age 57.7 ± 13.8 years, 37.2% male), 59 (13.8%) had GERD (10 endoscopically confirmed, 54 by AET ≥ 4%). Non-GERD accounted for 63.5% (n = 271), with 22.7% (n = 97) in the borderline group. MNBI correlated negatively with AET (r = −0.482, P < 0.01) and LA grade (r = −1.390, P = 0.005). The optimal MNBI threshold for GERD was 2167 Ω (sensitivity 0.86, specificity 0.75). Three LA grade A cases were reclassified as GERD-positive using this threshold.

Conclusion
MNBI significantly correlated with AET and LA grades, highlighting its diagnostic value in Korean GERD patients. However, regional variations suggest higher MNBI thresholds than Lyon 2.0 recommendations, warranting further studies to refine criteria for Asian populations.
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Key Words
Gastroesophageal reflux; Lyon Consensus 2.0; Mean nocturnal basal impedance

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Introduction

Gastroesophageal reflux disease (GERD) is a common disease and a major upper gastrointestinal problem in Western countries. Nevertheless, its reported prevalence among Asians is relatively low.[1-3] By contrast, time trend studies have also shown an increase in the prevalence of symptom-based GERD and endoscopic reflux esophagitis in Asia.[4]

Recent research has highlighted regional discrepancies in the normal values of esophageal impedance-pH metrics, including acid exposure time (AET) and mean nocturnal basal impedance (MNBI) of healthy asymptomatic subjects between Western and Asian populations.[5] A meta-analysis of 19 Asian studies involving asymptomatic subjects showed that the upper normal limit of AET was 3.2% (95% CI, 2.70-3.90%).[6] Consequently, the 2020 Seoul consensus on GERD proposed that AET ≥ 4.0% should be considered abnormally high in Asians.[7] This value is significantly lower than the AET threshold of > 6% defined by the Lyon consensus for GERD.[8] In addition, the median MNBI in the distal esophagus was significantly higher in Asia (median 3900 Ω, 2353-5667) compared to the Netherlands (median 2917 Ω, 2218-4162, $P < 0.001$).[5] On the other hand, no studies have been conducted on the differences in AET and MNBI among GERD patients in Asia.

The Lyon Consensus 2.0 (Lyon 2.0) updated its GERD diagnostic criteria. The key changes include recognizing Los Angeles (LA) grade B esophagitis as conclusive evidence for GERD. Moreover, the precise threshold of MNBI (< 1500 Ω) was provided as adjunctive or supportive evidence that increases confidence in the presence of pathologic reflux when other evidence is borderline or inconclusive for GERD, while a threshold of > 2500 Ω serves as evidence against pathologic reflux.[9]

This study examined the relevance of the Lyon 2.0 criteria in Korean patients, considering the relatively lower AET and higher MNBI values in Asians compared to Western populations.

Materials and Methods

Subject

This retrospective study was conducted at a tertiary medical center (Asan Medical Center, Seoul, South Korea) between January 2021 and August 2023. The study included all adult patients (age > 18 years) undergoing an evaluation for persistent esophageal or extra-esophageal symptoms suggestive of GERD, using endoscopy and ambulatory pH-impedance monitoring without anti-secretory medications. The patients were excluded if they had a history of foregut surgery, were diagnosed with major esophageal motility disorders, or if their studies were insufficient or incomplete. The demographic and clinical data were extracted from the patient records. The study protocol received approval from the Institutional Review Boards of the institutions (S2024-0199-0001).

pH-Impedance Studies and Metrics

Before undergoing 24-hour ambulatory pH-impedance monitoring (Diversatek Healthcare, Milwaukee, WI, USA), the patients were advised to discontinue proton pump inhibitor therapy for 7 days and stop using any histamine H2 blockers, prokinetic agents, or antacids 3 days before the test, in accordance with the international GERD consensus guidelines.[10] The patients arrived after fasting overnight. High-resolution manometry (Diversatek) was conducted to locate the proximal border of the lower esophageal sphincter, ensure that the distal pH sensor was positioned 5 cm above the lower esophageal sphincter, investigate motility disorders, and exclude major motor disorders. Throughout the pH impedance study, the patients maintained a diary of their food and drink consumption, as well as any symptoms. The total AET, which is defined as the percentage of time during the study that the distal esophagus was exposed to a pH below 4.0, was calculated after excluding mealtime periods.

The MNBI was calculated following the approach outlined by Martinucci et al,[11] which entailed extracting and averaging baseline impedance values during stable 10-minute intervals at 1:00 AM,

2:00 AM, and 3:00 AM. Previous studies reported that distal MNBI (measured at the 3-cm and 5-cm markers) correlates with the AET, whereas proximal MNBI does not.[12-14]

Gastroesophageal Reflux Disease Definition

The present study redefined definite GERD based on the updated Lyon 2.0 Consensus with LA classification B, C, or D or an AET of 4% or greater than the proton pump inhibitor according to the 2020 Seoul GERD consensus. An AET < 4%,[7] LA normal Z line or class A, and < 40 reflux episodes per day were defined as not GERD (non-GERD). Patients who did not fit into any group (definite GERD nor non-GERD) were defined as borderline GERD.

Statistical Methods

Unless stated otherwise, the data are presented as the means ± SEM. The continuous variables were analyzed using the two-tailed Student's *t* test, while the categorical variables were evaluated using a chi-square test. The Pearson correlation was used to assess the relationships between continuous variables. The concordance between the total AET and MNBI was determined. The receiver operating characteristic curves were generated to evaluate the predictive power of abnormal AET, abnormal MNBI, and either abnormal AET or MNBI for GERD. A *P*-value < 0.05 was considered significant. All statistical analyses and graphical representations were conducted using SPSS software version 26.0 (IBM Corp., Armonk, NY, USA).

Results

Baseline and Clinical Characteristics

Four hundred and twenty-seven patients fulfilled the inclusion criteria and were included in this study, with an average age of 57 years and 37.0% male (Table 1). Of these patients, 36.7%, 20.0%, and 41.6% had esophageal symptoms (reflux or heartburn), extra-esophageal symptoms (globus, sore throat, and hoarseness), and both, respectively. Ninety-three percent of patients were in the LA grade normal (no esophagitis); 4.2%, 1.9%, 0.2%, and 0.0% were grade A, B, C, and D, respectively. Most patients (86.0%) had an AET below 4.0%; 5.8% had an AET between 4.0% and 6.0%, and 7.4% had an AET > 6%.

Table 1. Basic and Clinical Characteristics of Enrolled Patients

Variable	Total (N = 427)
Age (yr)	57 ± 13
Male	159 (37.2)
Symptom	
Esophageal (reflux or heartburn)	158 (37.0)
Extra-esophageal	86 (20.1)
Both	179 (41.9)
LA classification	
0	400 (93.7)
A	18 (4.2)
B	8 (1.9)
C	1 (0.2)
AET category	
< 4%	370 (86)
4-6%	25 (5.8)
> 6%	32 (7.4)

LA, Los Angeles.
Data are presented as mean ± SD for continuous variables or as n (%) for categorical variables.

Table 2. Multichannel Intraluminal Impedance-pH Characteristics of Patients With Gastroesophageal Reflux Disease, Borderline, and Non-gastroesophageal Reflux Disease

Variable	Definite GERD (n = 61)	Borderline GERD (n = 95)	Non-GERD (n = 271)	*P*-value
Age (yr)	59.4 ± 12.9	55.9 ± 16.3	58.0 ± 13.0	0.305
Gender (male)	32 (54.2)	57 (58.8)	70 (25.8)	< 0.001
AET (%)	7.2 ± 4.1	1.2 ± 1.1	0.6 ± 0.8	< 0.001
MNBI (Ω)	1426.6 ± 788.5	2720.7 ± 879.6	2841.2 ± 989.1	< 0.001
Reflux episode (n)	47.6 ± 25.4	55.6 ± 22.2	21.1 ± 10.1	< 0.001
LA-classification				
0	50 (82.0)	90 (94.7)	260 (95.9)	< 0.001
A	2 (3.3)	5 (5.3)	11 (3.1)	< 0.001
B	8 (13.1)	0 (0.0)	0 (0.0)	< 0.001
C	1 (1.6)	0 (0.0)	0 (0.0)	< 0.001

Data are presented as mean ± SD for continuous variables or as n (%) for categorical variables.

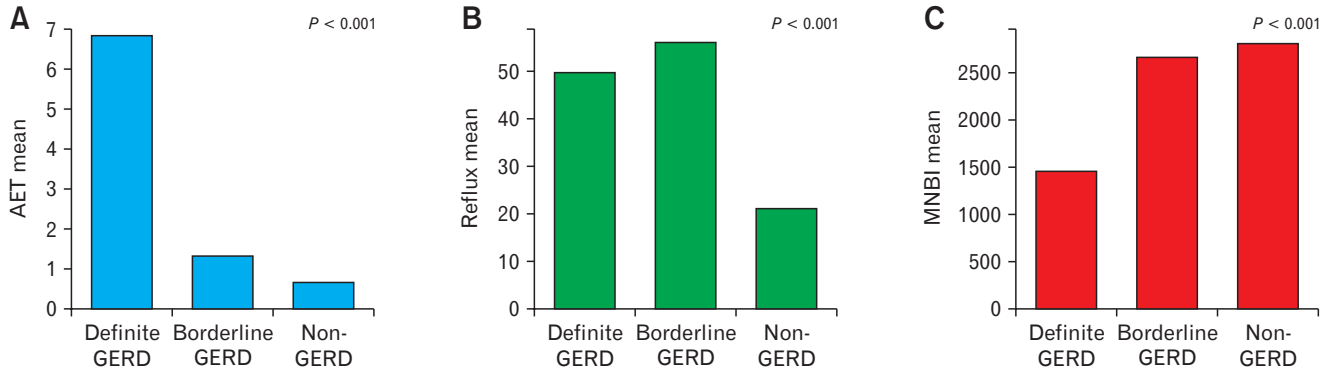

Figure 1. Comparison of mean acid exposure time (AET; A), numbers of reflux episodes (B), mean nocturnal baseline impedance (MNBI; C) according to non-gastroesophageal reflux disease (GERD), borderline GERD, and definite GERD.

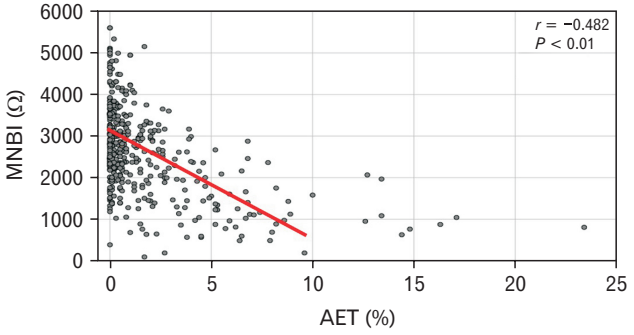

Figure 2. Correlation between the mean nocturnal baseline impedance (MNBI) and acid exposure time (AET).

Clinical Characteristics According to Redefined Definite, Borderline, Non-gastroesophageal Reflux Disease Groups

According to the study definition, 61, 95, and 271 patients were classified as having definite GERD, borderline GERD, and non-GERD, respectively. Significant differences in LA classification were observed between groups ($P < 0.001$), with higher grades of esophagitis (LA grade B or C) predominantly observed in the definite GERD group. On the other hand, LA grade A did not show any significant difference among the non-GERD, borderline GERD, and definite GERD patients (Table 2).

Definite GERD patients had significantly higher AET values (7.2 ± 4.1%) than the borderline (1.2 ± 1.1%) and non-GERD patients (0.6 ± 0.8%) ($P < 0.001$) (Fig. 1A). Borderline GERD patients (55.6 ± 22.2/day) had significantly more reflux episodes compared to definite GERD (47.6 ± 25.4/day) and non-GERD patients (21.1 ± 10.1/day, $P < 0.001$) (Fig. 1B). MNBI values were significantly lower in definite GERD patients (1426.6 ± 788.5 Ω) than the borderline (2720.7 ± 879.6 Ω) and non-GERD (2841.2 ± 989.1 Ω) patients ($P < 0.001$) (Fig. 1C).

Clinical Correlation Between Mean Nocturnal Baseline Impedance, Acid Exposure Time, and Los Angeles Classification

A negative correlation was observed between MNBI and AET ($r = -0.482$, $P < 0.01$), meaning MNBI decreased as the AET increased (Fig. 2). We conducted a subgroup analysis to examine whether the correlation between AET and MNBI differs based on AET categories: AET < 4, 4 ≤ AET < 6, and AET ≥ 6. Subgroup analysis revealed a significant correlation between AET < 4% and MNBI ($r = -2.92$, $P < 0.01$) (Fig. 3A). However, the correlation was weaker in the 4% ≤ AET < 6% group (Fig. 3B) and non-significant in AET ≥ 6% group (Fig. 3C). A negative correlation was also observed between the MNBI and the LA classification of esophagitis severity ($r = -1.450$, $P = 0.003$) (Fig. 4).

Diagnostic Threshold of Mean Nocturnal Baseline Impedance to Predict Abnormal Acid Exposure Time (Acid Exposure Time ≥ 4%)

This study examined whether MNBI can predict patients with pathologic AET (AET ≥ 4%) vs non-pathologic AET (AET < 4%). The optimal MNBI threshold for diagnosing GERD in patients with AET ≥ 4% was 2167 Ω when constructing receiver operating characteristic curves evaluating abnormal MNBI in predicting AET ≥ 4%. The sensitivity and specificity for this threshold were 0.86 and 0.77, respectively, indicating that it is a strong diagnostic marker for GERD (Fig. 5).

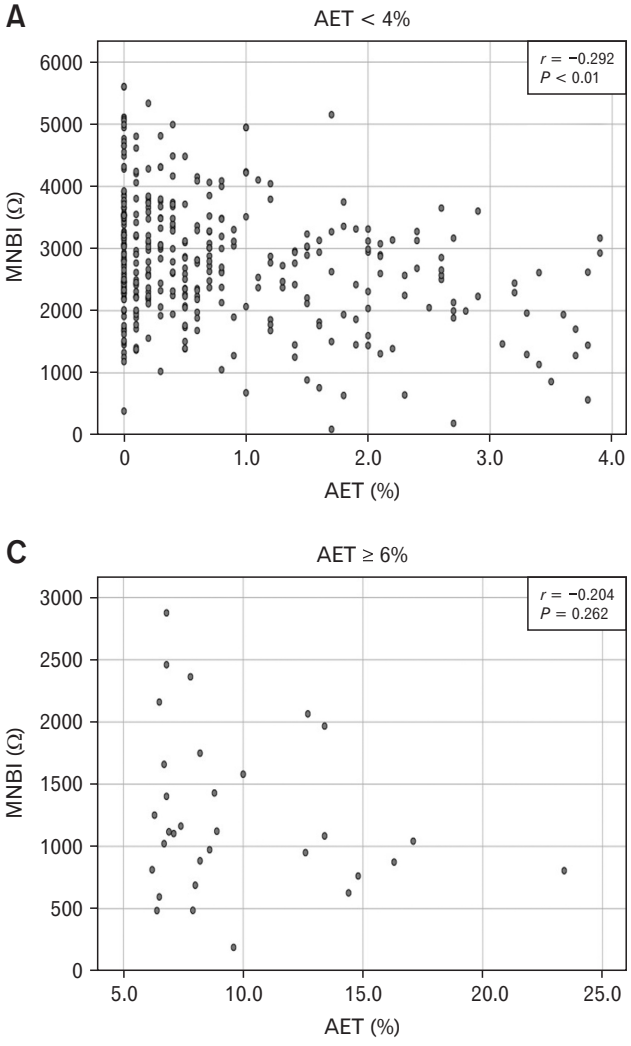

Figure 3. Correlation between the mean nocturnal baseline impedance (MNBI) and acid exposure time (AET) under subgroup analysis according to AET (< 4% [A], 4% ≤ 6% [B], ≥ 6% [C]).

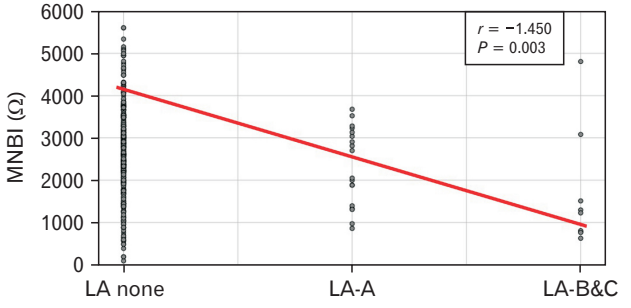

Figure 4. Correlation between the mean nocturnal baseline impedance (MNBI) and Los Angeles (LA) classification.

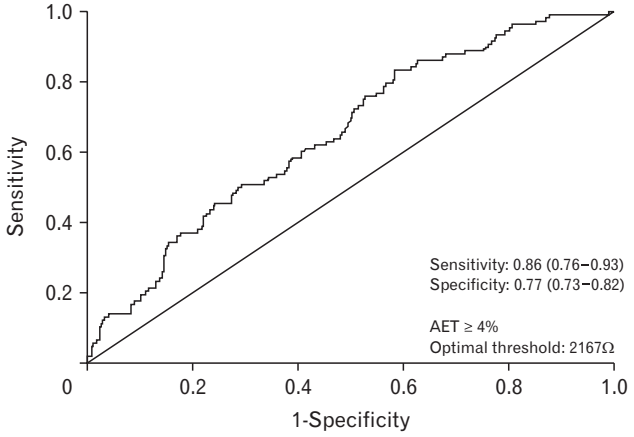

Figure 5. Receiver operating characteristic (ROC) curves showing that a low mean nocturnal baseline impedance (MNBI) has the best clinical value in predicting when the acid exposure time (AET) is more than 4%.

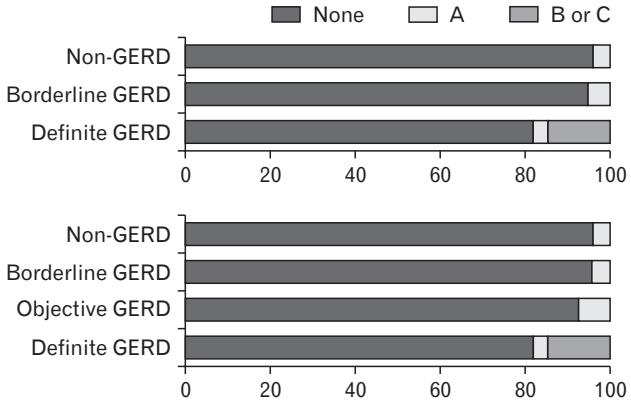

Figure 6. Changes in the proportion of Los Angeles classification grade A (LA-A) after reclassifying gastroesophageal reflux disease (GERD) by adding mean nocturnal baseline impedance (MNBI) cutoff.

Reclassification After Adding the Acid Exposure Time Threshold

The patients were reclassified by incorporating the MNBI cutoff criteria, resulting in changes to the distribution of patients with LA grade A esophagitis across the definite GERD, borderline, and non-GERD groups. Three cases of LA grade A were reclassified as objective GERD from borderline GERD after redistributing the objective GERD group (AET < 4% with MNBI < 2167 or reflux episodes > 80/day) from the borderline GERD category by applying the MNBI cutoff. With the inclusion of the MNBI cutoff level, more LA grade A cases were redistributed within the GERD category (including definite and objective GERD), increasing from 3.3% to 12.8% (Fig. 6).

Discussion

This study identified a significant correlation between the MNBI values, AET, and LA classification progression from grade A to C in patients with persistent GERD-like symptoms. Definite GERD was redefined as AET ≥ 4% or LA grade B, C, or D, considering regional differences in AET and MNBI values. In addition, re-applying the optimal MNBI threshold of 2167 Ω (AET ≥ 4%) resulted in a more frequent re-categorization of LA grade A within the GERD group.

Despite enrolling patients with GERD-like symptoms, only a small subset of the 427 patients met the Lyon 2.0 criteria for a definite GERD diagnosis. Specifically, only 42 patients (9.8%) qualified, comprising 13 patients with LA grade B or higher, 32 patients with AET ≥ 6%, and 3 patients who met both criteria. In particular, there were no patients with LA grade D, and only 1 patient presented with grade C esophagitis. Owing to its low prevalence, definite GERD was defined as AET ≥ 4% based on the 2020 Seoul GERD consensus[7] or as having LA grade B or higher according to the Lyon 2.0 criteria.[9] Sixty-one patients were reclassified after redefining definite GERD.

The incorporation of impedance technology suggests that mechanisms other than acid reflux may be involved in developing reflux symptoms,[15] but their accuracy can be affected by factors such as swallowing, reflux episodes, meals, and artifacts. Martinucci et al,[11] overcame these confounders by calculating the mean baseline impedance during 3 nocturnal sleep periods when the values were more stable. With the proven significance of MNBI and the strong correlation with AET, the Lyon 2.0 consensus introduced MNBI as adjunctive or supportive evidence, providing precise thresholds. An MNBI value of < 1500 Ω was suggested as the diagnostic approach for pathologic reflux (AET ≥ 6%), while an MNBI value of > 2500 Ω is presented as evidence against GERD (AET < 4%).[9]

Considering regional variations, Korean patients were expected to require a higher MNBI threshold for GERD diagnosis than what is recommended by the Lyon 2.0 guidelines.[5] In the present study, in predicting AET ≥ 4%, the optimal MNBI threshold was 2167 Ω. On the other hand, the same MNBI threshold value of 2167 Ω was identified for distinguishing definite GERD from borderline GERD and borderline GERD from non-GERD. The different threshold values were not identified for each group because of the lack of negative control data from non-symptomatic healthy individuals. Patel et al,[13] found that MNBI has low specificity in differentiating GERD from reflux hypersensitivity. Further research will be needed to establish more refined MNBI threshold values to better differentiate the 3 groups (definite GERD vs borderline GERD vs non-GERD) by including the values from asymptomatic healthy individuals. Otherwise, factors such as body mass index likely contribute to these differences; however, the retrospective design resulted in substantial body mass index data loss, limiting reliable correlation analysis. Further research is needed to elucidate their impact.

The strong correlation between MNBI and AET has been well-established.[13,14] In the present study, a significant negative correlation was observed between MNBI and AET (Fig. 2). After conducting subgroup analysis, the association with MNBI tends to decrease as the AET level rises. The correlation was significant when AET was < 4%, with $r = -2.920$ and $P < 0.01$. On the other hand, the correlation was weaker when AET was between

4% and 6% ($r = -0.347$, $P = 0.090$), but no significant correlation was noted for AET ≥ 6% ($r = -0.204$, $P = 0.262$).

This study also had some limitations. First, because of the absence of data from healthy asymptomatic subjects, it may be more appropriate to consider the MNBI threshold as a diagnostic criterion for distinguishing between GERD and functional heartburn or reflux hypersensitivity. Second, before applying the MNBI threshold, LA grade A was observed more frequently in the borderline GERD group than in the definite GERD group. On the other hand, after applying the MNBI threshold, LA grade A was reclassified more frequently within the GERD group. Larger, more comprehensive studies will be needed to refine the MNBI criteria for diagnosing pathological reflux in Asian populations because LA grade A is not yet fully classified as pathologic GERD. Nevertheless, these data suggest the potential utility of MNBI in distinguishing GERD patients from borderline or non-GERD individuals and support the integration of impedance-pH measurements with traditional AET metrics for GERD diagnosis.

In conclusion, MNBI also strongly correlated with the AET and LA grades in Korean patients. Considering regional differences and the updates in the Lyon 2.0 criteria, a new definition for GERD was developed for the Korean population, and the corresponding MNBI threshold was established. Larger studies will be needed to refine the MNBI criteria for pathological reflux in Asian populations.

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Conflicts of interest: None.

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