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Demographic and Manometric Variables Can Independently Predict Gastroesophageal Reflux Disease: The AGES-D Score

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Objectives: Conclusive diagnosis of gastroesophageal reflux disease (GERD) can be challenging. When reflux monitoring is inconclusive, high-resolution esophageal manometry (HRM) may provide additional relevant information. We aimed to identify demographic and manometric parameters associated with GERD and to propose a diagnostic score. **Methods:** Adult patients with GERD symptoms who underwent reflux monitoring and HRM were considered for inclusion. The gold standard for GERD diagnosis was acid exposure time (AET); patients with AET>6% and AET<4% were included. Univariate and multivariate analyses were performed. A diagnostic score was developed using parameters independently associated with GERD. Generation and validation cohorts were randomly selected in a 2:1 ratio. Diagnostic accuracy was assessed using the area under the receiver operating characteristic curve (AUC ROC). **Results:** A total of 391 patients met the inclusion criteria; 167 had GERD (AET>6%) and 224 did not have GERD (AET <4%). In the multivariate analysis, age, male sex, and the distance between the lower esophageal sphincter and the crural diaphragm (LES-CD) were directly associated with GERD, while esophagogastric junction contractile integral (EGJ-CI) and distal contractile integral (DCI) were inversely associated with GERD (*p* values: 0.03, <0.01, <0.01, 0.01, and 0.01, respectively). The AUC ROC of a diagnostic score based on these parameters was 0.76 and 0.82 in the generation and validation cohorts, respectively. **Conclusions:** In this observational study, age, male sex, LES-CD distance, EGJ-CI, and DCI (AGES-D) were independently associated with GERD. A novel score incorporating these parameters could be useful in the assessment of inconclusive cases.

Keywords Esophagogastric junction; Gastroesophageal reflux; Esophageal pH monitoring; Manometry.

INTRODUCTION

Gastroesophageal reflux disease (GERD) is a common condition with a significant economic burden and impact on quality of life.[1,2] Its reported prevalence ranges from 2.5% in China to 51.2% in Greece, making it one of the most prevalent diseases in Western countries.[3]

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therapy as a diagnostic test for GERD can be inappropriate, as up to 35% of patients without evidence of GERD report symptomatic relief.[4,5] When upper endoscopy does not reveal an alternative diagnosis or confirmatory evidence of GERD,[6] reflux monitoring with pH or pH-impedance (pH±MII) off PPI therapy is recommended to confirm the diagnosis.[7] Esophageal acid exposure time (AET) is the most reproducible and widely accepted measurement to define abnormal esophageal reflux burden.[7-9] According to the Lyon consensus, an AET>6% is diagnostic of GERD, while an AET<4% rules it out.[10,11] Indeterminate pH±MII results (AET 4%–6%) present a diagnostic challenge and require additional evidence to confirm pathological GERD.[10] In this context, various high-resolution esophageal manometry (HRM) and reflux monitoring metrics have been proposed to optimize GERD diagnosis.[12-15]

Recently, scoring systems incorporating clinical features, symptoms, manometric findings, and pHmetry have been developed and are being used as adjuncts in the diagnosis of GERD, such as the COuGH RefluX Score,[16] the Milan Score,[17] and, more recently, the Lyon Score.[18] However, the validation and clinical utility of these scores in diverse populations are ongoing, and their applicability to the Latin American population remains unknown. Moreover, some of these scores emphasize laryngeal symptoms, while others include variables such as leg elevation, for which variability and reproducibility remain uncertain.

Thus, the aim of this study was to identify demographic and manometric variables independently associated with GERD and to propose a score to assist in the diagnosis of challenging cases.

METHODS

Patient selection

This was an observational, retrospective study. All adult patients with GERD symptoms who underwent HRM and concomitant pH or pH-impedance monitoring at the UC-CHRISTUS Digestive Physiology Laboratory were eligible for inclusion during a 10-year period (2010-2020). Patients with previous esophageal and/or gastric surgery, concomitant use of PPI (ON-PPI studies), obstructive and major motor disorders according to the Chicago Classification V3.0,[19] and those with AET in the undetermined range (4%–6%)[10] were excluded from the analysis. The gold standard for the diagnosis of GERD was the AET during ambulatory reflux monitoring.[10] Patients with AET>6% were included in the GERD group, and patients with AET<4% were included in the non-GERD group. The study protocol was approved by the Pontificia Universidad Católica Institutional Review Board (ID Protocol 14-011). Informed consent is part of a waiver included in the protocol approved by the Pontificia Universidad Católica de Chile.

High-resolution manometry

All studies were performed in the supine position after at least 8 h of fasting, and medications potentially affecting motor function were temporarily held. HRM was performed using a ManoScan 360 Catheter (36 channels spaced 1 cm apart, Sierra Scientific Instruments). The catheter was inserted transnasally and positioned to record from the hypopharynx to the stomach. The manometric protocol included a 5-min resting period to evaluate basal sphincter pressure and ten 5 mL water swallows. Topographic analysis was performed using ManoView ESO 3.3 software (Given Imaging). Interpretation was done according to the Chicago Classification criteria V3.0.[19] Distal contractile integral (DCI; mm Hg·s·cm) was used to quantify esophageal body contraction vigor, Integrated Relaxation Pressure (IRP; mm Hg) to evaluate esophageal outflow obstruction, and distal latency (DL; s) to measure the interval between upper esophageal sphincter relaxation and the Contractile Deceleration Point.

Morphology of the esophagogastric junction (EGJ) was characterized by assessing the relationship between the lower esophageal sphincter (LES) and crural diaphragm (CD), as previously suggested.[19] Type 1 EGJ morphology corresponds to superimposed LES and CD. Axial separation <3 cm defined type 2, and ≥3 cm defined type 3 (hiatal hernia).[19,20] The esophagogastric junction contractile integral (EGJ-CI; mm Hg·cm) was measured according to Nicodème et al.[15] The DCI box was placed at the EGJ, encompassing the LES and CD, over three complete respiratory cycles above the gastric baseline pressure. The calculated contractile integral was then divided by the duration of the three respiratory cycles to make it time-independent, and it was measured in mm Hg·cm. Only the resting or landmark phase was analyzed.[21] In the case of type 3 hiatal hernia EGJ, only the LES component was considered for the EGJ-CI calculation.[10]

All studies were analyzed simultaneously by two researchers (P.R. and H.M.). Discrepancies were resolved by consensus.

Ambulatory 24-hour reflux monitoring

Studies performed OFF antisecretory therapy for at least 10 days were included. HRM was used to localize the proximal margin of the LES, and a probe was placed with the pH sensor 5 cm proximal to the LES. AET was defined as the fraction of time the pH was <4.0 during ambulatory pH or pH-impedance monitoring.[6] Total AET was extracted, and values <4.0% were considered normal. AET>6% was considered indicative of pathologic GERD.[10] Reflux-symptom association using

Symptom Index (SI) and Symptom Association Probability (SAP),[22] as well as the Johnson-DeMeester Score,[23] were also analyzed. Impedance-based metrics were not assessed for this study.

Data analysis

Continuous data are described using means and standard deviations or medians and interquartile ranges (IQR), according to their distribution. The Kolmogorov–Smirnov test was used to assess normality. Assuming that about 60% of patients with symptoms have pathological reflux monitoring,[24] the study required a sample size of 385 to estimate the expected proportion with 5% absolute precision and 95% confidence.

Student's t-test and the Mann–Whitney U test were used to compare parametric and non-parametric data, respectively. Categorical data are presented using proportions and percentages and compared using the chi-square or Fisher exact test. A multivariate logistic regression analysis was performed to adjust for confounding factors. IRP, EGJ-CI, DCI, and LES-CD distance were included in the regression model based on their physiological relevance. Additionally, all parameters with a *p*-value <0.2 in the univariate analysis were included.[25] In the regression model, associations were considered significant at a *p*-value <0.05. Parameters independently associated with GERD in the multivariable analysis were used to build a diagnostic score. The study sample was randomized 2:1 into generation and validation cohorts. In the generation cohort, a multivariable logistic regression was performed, and the estimates of the intercept and each independently associated parameter were used to construct the diagnostic score. The predictive performance of the score was evaluated using the area under the receiver operating characteristic curve (AUC ROC). An optimal cutoff value was determined based on Youden's index to maximize both sensitivity and specificity for GERD diagnosis. The score and optimal cutoff were then applied to the validation cohort. AUC ROC, sensitivity, specificity, positive and negative predictive values were calculated to assess the diagnostic performance of the proposed score. All analyses were performed using SAS University Edition (SAS/STAT®; SAS Institute Inc.).

RESULTS

General statistics

A total of 556 patients were studied, of which 391 met the inclusion criteria. 167 patients had AET>6% and were included in the GERD group (87 women, mean age 51.5 years), and 224 patients with AET<4% were included in the non-GERD group (171 women, mean age 48.3 years).

In the GERD group, 111/167 (66.5%) had a normal manom-

Table 1. Univariate analysis of demographics and HRM variables

	GERD, AET>6% (n=167)	Non-GERD, AET<4% (n=224)	*p*-value
Age (yr)	52±13	48±14	<0.01*
Gender, male	80 (48)	53 (25)	<0.01**
HRM			
IRP (mm Hg)	5 (2–8)	7 (4–9)	<0.01***
DCI (mm Hg·s·cm)	808 (451–1354)	1407 (717–2186)	<0.01***
DL (second)	6.8 (6–8)	6.6 (6–8)	0.60***
LES-CD (mm)	20 (0–35)	0 (0–21)	<0.01***
EGJ morphology			
Type 1	55 (33)	126 (56)	
Type 2	25 (15)	33 (15)	
Type 3	87 (52)	65 (29)	0.01***
EGJ-CI (mm Hg·cm)	15.2 (5–28)	32.6 (20–54)	<0.01***
Reflux monitoring			
No. reflux events	114 (71–167)	35 (21.5–59)	<0.01***
JDS	39 (29.4–60)	5.8 (3–10)	<0.01***
SI (%)	91 (60–100)	31 (0–75)	<0.01***
SAP (%)	99.4 (88.7–100)	89.8 (99.5–100)	<0.01***

Data are presented as mean±standard deviation, n (%), or median (interquartile range).
*t-test; **chi-square; ***Mann–Whitney U Test.
HRM, high-resolution manometry; GERD, gastroesophageal reflux disease; AET, acid exposure time; IRP, integrated relaxation pressure; DCI, distal contractile integral; DL, distal latency; LES-CD, lower esophageal sphincter-crural diaphragm distance; EGJ, esophagogastric junction; EGJ-CI, esophagogastric junction contractile integral; JDS, Johnson DeMeester Score; SI, Symptom Index; SAP, Symptom Association Probability.

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etry, 55/167 (32.9%) had ineffective esophageal motility (IEM), and 1/167 (0.6%) had fragmented peristalsis. In the non-GERD group, 188/224 (83.9%) had a normal manometry (p<0.01). Median AET was 9.9% in the GERD group and 1.2% in the non-GERD group (p<0.01).

Univariate analysis

Table 1 shows all variables included in the univariate analysis. Among categorical variables, men had a higher prevalence of GERD compared to women (60.1% vs. 33.7%; p<0.01). Patients with type III EGJ on HRM also had more GERD (57.5% vs. 33.3%; p<0.01). GERD patients were significantly older than non-GERD patients (52 years vs. 48 years; p<0.01).

Regarding manometric variables, GERD patients had a significantly greater LES-CD distance (20 mm vs. 0 mm; p<0.01), a significantly lower mean IRP (5 mm Hg vs. 7 mm Hg; p<0.01), and a significantly lower mean DCI (808 mm Hg·s·cm vs. 1407 mm Hg·s·cm; p<0.01). There was no significant difference in DL (6.8 s vs. 6.6 s; p=0.60). The presence of a minor disorder of peristalsis was associated with GERD (p<0.01). The median EGJ-CI was 15.2 (IQR 5–28) mm Hg·cm in the GERD group and 32.6 (IQR 20–54) mm Hg·cm in the non-GERD group, which was statistically significant (p<0.01).

For pH monitoring variables, the GERD group had a significantly higher number of reflux events (114 vs. 35; p<0.01), as well as higher Johnson-DeMeester Score, SI, and SAP values (p<0.01 for all).

Multivariate analysis

Table 2 shows the variables included in the multivariate analysis. Age, sex, LES-CD distance, EGJ-CI, and average DCI were independently associated with GERD (c=0.78). Both EGJ-CI and average DCI were negatively associated; higher values were linked to a lower risk of GERD (Table 2). EGJ-CI was significantly lower in the GERD group compared to the non-GERD group (p<0.001). The AUC ROC of EGJ-CI for GERD diagnosis was 0.73. Using an optimal cutoff value of 28.7 mm Hg·cm, the sensitivity and specificity were 77% and 59%, respectively (Fig. 1).

Table 2. Multivariable analysis of demographics and HRM variables

Predictor	Adjusted OR (95% CI)	Test statistic	p-value
Omnibus likelihood ratio		101.70	<0.01
Age	1.0 (1.00–1.04)	4.71	0.03
Male gender	3.4 (2.00–5.60)	22.90	<0.01
LES-CD	1.0 (1.01–1.04)	11.80	<0.01
IRP	1.0 (0.92–1.08)	0.01	0.95
EGJ-CI	0.9 (0.97–0.99)	6.86	0.01
DCI	1.0 (0.99–1.00)	6.83	0.01
HRM: minor disorder of peristalsis	1.4 (0.75–2.53)	0.90	0.34

C-statistic 0.78.
HRM, High-resolution manometry; LES-CD, lower esophageal sphincter-crural diaphragm distance; IRP, integrated relaxation pressure; EGJ-CI, esophagogastric junction contractile integral; DCI, distal contractile integral; OR, odds ratio; CI, confidence interval.

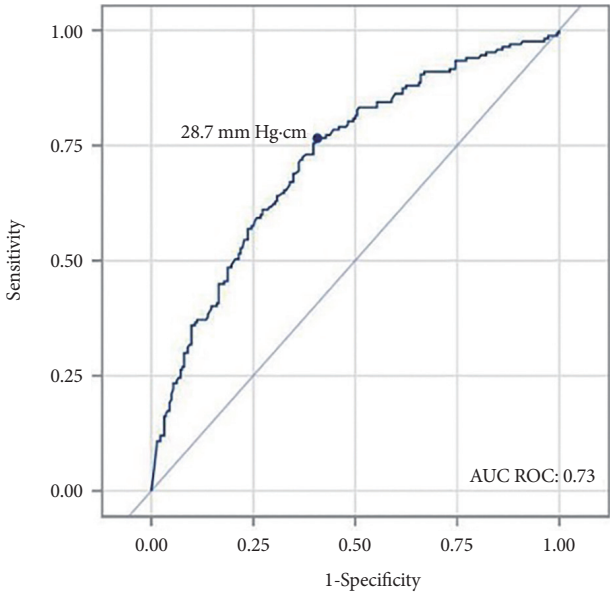
Generation and validation cohorts

For score generation, 261 and 130 patients were randomly assigned to the generation and validation cohorts, respectively. In the generation cohort, logistic regression was performed using the variables that were independently associated with GERD: age, sex, EGJ-CI, LES-CD distance, and mean DCI (Table 3).

The proposed score is:

AGES-D score=-0.6162+(age [years]×0.0222)+(0.5917 if male gender/0 if female gender)+(LES-CD [mm]×0.02298)-(EGJ-CI [mm Hg·cm]×0.01771)-(DCI [mm Hg·s·cm]×0.00037183).

Using the Youden index,[26] the suggested cutoff point was ≥0.125, with a sensitivity of 73% and a specificity of 75% for



EGJ-CI	Sensitivity	Specificity	PPV	NPV
Cutoff ≤28.7 mm Hg·cm	76.65%	59.38%	58.45%	77.93%

Fig. 1. ROC curves for EGJ-CI with their respective diagnostic performances and proposed cutoff. EGJ-CI, esophagogastric junction contractile integral; PPV, positive predictive value; NPV, negative predictive value; AUC ROC, area under the receiver operating characteristic curve.

the diagnosis of GERD (Fig. 2). Score performance analysis revealed an AUC ROC of 0.76 and 0.82 in the generation and validation cohorts, respectively (Fig. 2).

DISCUSSION

In this study, we found that combining clinical and manometric variables can aid in diagnosing inconclusive GERD in a Latin American population—a method we have incorporated into what we term the AGES-D score. AGES-D is an acronym that integrates five key elements for clinical and diagnostic evaluation in esophageal disorders: age, sex, EGJ, LES, and DCI. This framework enables a systematic analysis that combines demographic data with functional and anatomical findings, providing a comprehensive tool for addressing conditions such as GERD or esophageal motility disorders.

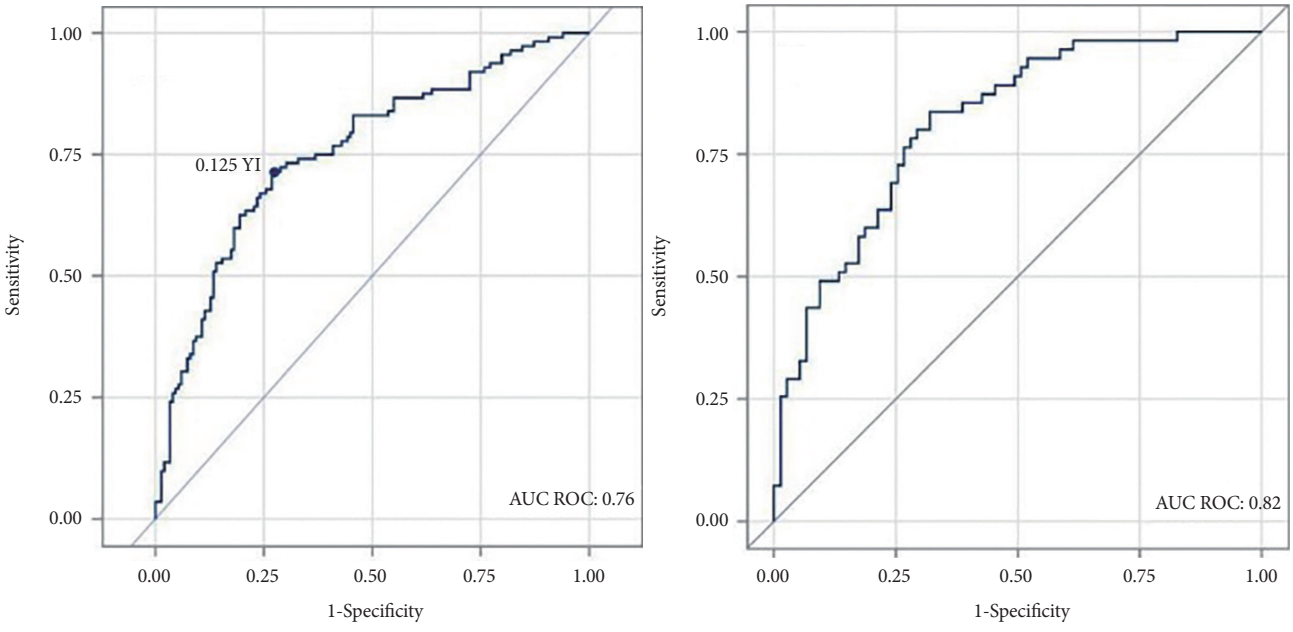
Table 3. Multivariate analysis in the generation cohort

Predictor	Adjusted OR (95% CI)	Test statistic	*p*-value
Omnibus likelihood ratio		56.8	<0.01
Age	1.0 (1.00–1.04)	3.9	0.05
Male gender	3.3 (1.80–5.90)	14.9	<0.01
LES-CD	1.0 (1.00–1.04)	6.4	0.01
EGJ-CI	0.9 (0.97–0.99)	6.3	0.01
DCI	1.0 (0.99–1.00)	4.6	0.03

C-statistic 0.76.
LES-CD, lower esophageal sphincter-crural diaphragm distance; EGJ-CI, esophagogastric junction contractile integral; DCI, distal contractile integral; OR, odds ratio; CI, confidence interval.

Our data show that the likelihood of GERD increases with age, which is consistent with the literature, where most studies establish a cutoff point near 50 years of age.[3] In the proposed model, a more precise relationship can be noted, with the OR increasing year by year. With respect to sex, this variable carried important weight in our cohort, which is not commonly observed in epidemiological studies based on reflux symptom surveys.[3] This may be owing to the female predominance of functional esophageal disorders, where symptoms suggestive of reflux may be present despite normal AET.[27] Therefore, it is not recommended to conclude a definitive diagnosis of GERD based on symptoms alone.[10]

The contractile performance of the esophageal body, measured by the DCI, can be classified as preserved or IEM.[19,28] As the relationship between GERD and esophageal hypomotility can be bidirectional,[29,30] the presence of IEM may be both a cause and a consequence of GERD. Our data confirmed that esophageal peristaltic vigor is a factor that may support GERD diagnosis. We found that the average DCI, but not the presence of minor peristalsis disorders (mainly IEM), behaved as an independent predictor of pathological AET. This may be owing to the current IEM criteria lacking stringency, as several studies have reported the presence of IEM in healthy indi-



	GERD-score derivation cohort	Sensitivity	Specificity	PPV	NPV
A	Cutoff ≥0.125	71.4%	72.5%	66.1%	77.1%

	GERD-score validation cohort	Sensitivity	Specificity	PPV	NPV
B	Cutoff ≥0.125	72.7%	74.7%	67.8%	78.9%

Fig. 2. ROC curves for GERD-score generation (A) and validation (B) cohorts with their respective diagnostic performances. GERD, gastroesophageal reflux disease; PPV, positive predictive value; NPV, negative predictive value; AUC ROC, area under the receiver operating characteristic curve.

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viduals.[31] More importantly, as the relationship between hypomotility and acid burden is linear, any cutoff used to define IEM would be somewhat arbitrary. The use of a continuous variable like DCI may therefore be more appropriate.

The EGJ is an anatomically complex structure composed of the LES and CD, both of which are relevant components of the functional barrier between the esophagus and the stomach.[32,33] Our data showed that both anatomical and functional characteristics are independently associated with GERD. Two HRM metrics have been proposed by current international consensus to assess EGJ barrier function.[10] The first is the structural dimension of the EGJ, which can be categorized based on the spatial relationship between the LES and CD.[14] Both the LES-CD distance and the classification of EGJ types 1, 2, and 3 were associated with the presence of GERD. We chose the LES-CD distance to represent EGJ anatomy in the score, as higher EGJ types are associated with progressively reduced diagnostic performance. Moreover, GERD prevalence was significantly different only when comparing type II to type I. Thus, LES-CD distance provides a more precise and detailed metric.

The EGJ-CI is an index determined similarly to DCI and is calculated by dividing the DCI value by the duration of three complete respiratory cycles.[15] Our data show that both anatomical and functional EGJ barrier evaluation metrics were independently correlated with acid burden. Deterioration of the EGJ, both functionally and anatomically, may promote GERD during exercise.[34] Additionally, our data suggest that EGJ-CI, rather than basal EGJ pressure, is independently associated with acid burden. This may be because EGJ-CI better reflects both inspiratory and expiratory pressure components, and prior studies have reported that the diaphragmatic contribution is relevant in both phases of respiration.[15,35] Consistent with our findings, Wang et al.[36] demonstrated that EGJ-CI negatively correlates with reflux burden, including total reflux episodes and AET, and may reflect dysfunction of the antireflux barrier.[37]

Although previous studies have proposed EGJ-CI cutoff values for GERD diagnosis,[38,39] many of these use gold standards different from currently accepted definitions, such as AET >4%, supine AET, reflux episode counts, or symptom association metrics.[39] Conversely, our cohort used the most recent diagnostic criteria, and EGJ-CI demonstrated good diagnostic performance both on its own (with a cutoff of 28.7 mm Hg·cm) and as part of the proposed score. This cutoff is lower than the one reported by Nicodème et al.[15] (39 mm Hg·cm).

The exclusion of patients with inconclusive AET (4%–6%) was a deliberate methodological decision aimed at developing the score based on phenotypically distinct groups, thereby improving predictive accuracy. However, the AGES-D score is intended for clinical application specifically in those indeterminate cases. We acknowledge that a limitation of our study is the lack of clinical follow-up data, such as treatment response. Therefore, prospective studies are required to validate the score against clinical endpoints, which will be important for establishing its role in patient management.

We excluded pH-metric variables like reflux event counts from the multivariate model, as the AGES-D score is intended to complement pHmetry by focusing on manometric and demographic data, especially in inconclusive cases. Certain variables lost significance owing to collinearity (e.g., hiatal hernia and EGJ metrics), so we retained only those with independent predictive value, in line with recommended modeling practices.[25]

Compared to other recently published scores, such as the Milan, COuGH RefluX, or Lyon scores,[16-18] AGES-D does not rely on maneuvers like leg-raising, which can be difficult to standardize and lack clear supporting evidence. Nor does it depend on additional impedance metrics or symptoms like globus or cough. This makes the score simpler and more practical to apply. Moreover, our findings were demonstrated in a Latin American population, unlike the other scores, which have mainly been validated in European and Asian cohorts.

Among the limitations of this study, the retrospective design at a referral center may have introduced a selection bias toward more severe cases, and there was no standardized clinical follow-up. It could also be argued that the sensitivity and specificity of the score, around 70%–75%, is modest. However, the score is not intended to replace pHmetry in the diagnosis of GERD. Despite this, it showed a good AUC (0.82), which suggests that it meaningfully alters pre-test probabilities. Importantly, the variables used are already part of routine evaluations and do not involve additional cost, time, or procedures. Another limitation is that the score does not evaluate treatment response, unlike other recently published scores such as the Milan or Lyon scores.[17,18] Further studies are needed to evaluate whether AGES-D has predictive value in this regard. Finally, a key limitation is the lack of external validation. As the AGES-D score was developed and validated in a single Latin American population, future multicenter studies across diverse ethnic and clinical settings will be essential to confirm its broader utility.

Lastly, it is important to emphasize that this score is intended as a supportive tool in cases of indeterminate AET, to aid in selecting the appropriate therapy.

Authors' Contribution

Conceptualization: Hugo Monrroy. Data curation: Hugo Monrroy, Paula Rey, Ignacio Gran. Formal analysis: Ana Muñoz, Diego Reyes-Placencia,

Hugo Monrroy, Roberto Candia. Investigation: Ana Muñoz, Diego Reyes-Placencia, Hugo Monrroy. Methodology: Hugo Monrroy, Roberto Candia. Project administration: Hugo Monrroy. Resources: Hugo Monrroy. Supervision: Hugo Monrroy. Validation: Hugo Monrroy. Writing—original draft: Ana Muñoz, Diego Reyes-Placencia, Hugo Monrroy. Writing—review & editing: Hugo Monrroy, Roberto Candia, Paula Rey, Javier Chahuan, Ignacio Gran, José María Remes-Troche, Daniel Cisternas. Approval of final manuscript: all authors.

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