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Non-erosive gastroesophageal reflux disease determination criteria by functional tests: a predictive model based on multivariate analysis

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ABSTRACT

Background: Gastroesophageal reflux disease (GERD) in 2009 presented a prevalence of 11.5% in Venezuela. It is a complex, multifactorial disease that is difficult to define, since it consists of several signs and symptoms that may or may not coexist together, both in the presence and absence of the disease.

Methods: A prospective study was conducted that consisted of a group of 85 patients diagnosed with non-erosive gastroesophageal reflux disease (NERD) and 20 asymptomatic volunteers. Functional tests were conducted on both groups that included high resolution manometry, 24-hour pH-metry - impedance study. The chi-square independence test, principal component analysis and multiple correspondence analysis were applied to identify which variables showed greater association and importance for the diagnosis of NERD.

Results: The results indicated that it is possible to establish a rapid diagnostic test based on the solid drink test, distal contraction index, peristaltic jumps and presence of heartburn with a sensitivity of 96% and specificity of 90%.

Conclusions: It is possible to establish a NERD rapid diagnostic test based on functional tests.

Keywords: Gastroesophageal reflux disease, Non-erosive gastroesophageal reflux disease, Functional tests, Clearance, Principal component analysis, Multiple correspondence analysis

INTRODUCTION

Gastroesophageal reflux disease (GERD) is one of the most frequent causes of medical consultation, at least in the western world, with an estimated prevalence in Venezuela of 11.54%. GERD is a very complex and difficult to conceptualize disease, and should be seen more as a group of symptoms than as a simple entity, for example, when we talking about erosive disease, reference is made to a condition very different from regurgitation, which as the same time is very different from post nasal drip, chronic cough or non-cardiogenic precordial pain, however, all these entities correspond to the diagnosis of GERD accepted by most doctors, as established in the Montreal Consensus. The characteristic symptoms are heartburn

and regurgitation, but it may be associated with other presentations such as chest pain, chronic cough, hoarseness, laryngeal balloon and throat irritation. Clinical manifestations are not sufficient to establish the diagnosis of pathological reflux, and further examinations are necessary to confirm or deny GERD. The use of acid suppressive therapy (AST) has been used as a therapeutic test, and when the symptoms do not respond or there are alarm signals, it is necessary to carry out complementary tests.²

According to the Montreal consensus, the most symptomatic presentations are associated with evidence of tissue damage.² For many years, erosive GERD was considered the most common phenotype, however, according to the Vevey Consensus Group (2009), non-

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erosive disease constitutes approximately 70% of subpopulation, and is characterized by the presence of typical symptoms of reflux without visible mucosal lesion at endoscopy, with abnormal acid exposure time. Patients with non-erosive GERD (NERD) may experience similar symptoms in frequency and severity such as erosive GERD, since the symptoms and mucosal lesions do not necessarily coexist together.³ A proportion of patients with erosive esophagitis have no symptoms, while 50-85% of patients with typical reflux symptoms have no endoscopic evidence of erosive esophagitis and their response to AST is very poor.^{4,5}

Physiopathology of GERD is multifactorial and complex, with different mechanisms for generating symptoms. In the absence of AST, the episodes of reflux are mainly acidic, their duration and their proximal reach have a determining effect on the presentation of symptoms.^{5,6} Without the presence of acid, the damage to mucosal integrity expressed in dilation of intercellular spaces and esophagitis is almost null.⁷

Although there are many determining factors in its development, GERD is finally explained by the coexistence of three events: incompetence of the antireflux barrier, incomplete clearance of reflux gastric contents, and visceral hypersensitivity. The effectiveness of the anti-reflux barrier is dependent on anatomical elements: intrinsic sphincter, crural diaphragm, gastric girth, hiatal hernia, "pocket acid", gastric emptying, obesity, among others; while mechanical or volume clearance depends on high degree of integrity of the peristalsis of the esophageal body, so its deterioration contributes to an increase in acid exposure and plays an important role in the physiopathology of GERD. The most common pattern in patients with GERD is hypo contractility of the esophageal body, lower esophageal sphincter (LES), or both.^{8,9} It has been shown that absent or incomplete motility (hypo contractile peristalsis) is insufficient to maintain intra esophageal pressure and gastric esophageal pressure gradient resulting in poor clearance, likewise, hypo contractile esophagus and fragmented peristalsis are associated with a higher probability of erosive reflux.^{9,12,13} Several authors have shown that esophageal dysmotility in patients with erosive ERD not necessarily improve with the resolution of esophagitis, which suggests that the motor disorder is prior to GERD.^{14,15} In the same way, the motility of the esophageal body can improve after anti-reflux surgery.¹⁶ However, despite all this information, it has not been possible to establish whether motility disorder is the cause or consequence of GERD.

In order for swallowing to be effective, there are three conditions: continuity of the peristaltic wave, gradient of gastric esophageal pressure and relaxation of LES.¹³ Patients with reflux symptoms that do not respond to AST should have reflux monitoring, which includes pressure measurement and esophageal peristalsis due to high resolution (HRM), along with pHmetry and 24-hour

multichannel impedance (pHMCI), which allows to evaluate the pattern and vigor of esophageal contraction, gastric esophageal junction complex, distal latency, acid exposure time, proximal reach, association of symptoms, acid and non-acid reflux, and the identification of phenotypes in order to discard esophagus hypersensitive or functional heartburn.

The purpose of this research is to analyze the findings in a prospective experimental cohort study in symptomatic patients with and without suspected of NERD and correlate the results of the different functional tests applied in order to establish the contribution of each of them in the physiopathology of NERD, and also verify the possibility of establishing a more expeditious and economical diagnostic criteria for NERD based on the results of few functional tests.

METHODS

A cohort, prospective, observational, descriptive and correlational study was carried out in patients diagnosed as NERD. 85 patients (50 women) with an average age of 45.5 years (18-73) and 20 asymptomatic volunteers (10 women) with an average age of 38 years (20-57) were included, between the months of February 2013 to July 2019, evaluated at the Gastro Bariatric Clinic of Maracay, Aragua state. Venezuela, by the Gastroenterology service. NERD was defined by the presence of typical reflux symptoms without mucosal lesion visible at endoscopy. All patients underwent HRM and pHMCI on the same day, following the protocol of the research group specified in the previous publication.¹⁷ Interpretation of the HRM was made according to the Chicago Classification v3.0, classifying the strength of the contraction as normal, failed or weak and the contraction pattern as intact, premature or fragmented.18

Volunteers filled out the GERD questionnaire. All the patients included signed the informed consent. All subjects underwent Video Gastroscopy (VG), HRM and pHMCI. VG was performed with Fujinon ® FICE 4450HD instrument under sedation with Propofol assisted by anesthesiologist. Diagnosis of hiatal hernia (HH) was based on the classification of Hill modified by Kahrilas.¹⁹ was performed with 22-sensor Medical Measurement Systems ® (Enschede, NL) water perfusion equipment, progressing the transducer through the nasal passage to the stomach with the patient fasting, and included multiple swallow test with 200 ml of water to determine the functional reserve of the esophagus.²⁰ 10 drinks of 5 ml, 5 drinks of 10 ml of water to evaluate the peristalsis of the esophageal body, 5 drinks of 5 ml of viscous liquid and 2 solid drinks (10 grams) to evaluate the response of the esophageal body, and correlate the severity of motor alterations with the severity of GERD.²⁰ The pHMCI electrode was progressed nasally and positioned 5 cm above the proximal limit of the LES. In this position the impedance was measured at 3, 5, 7, 9, 15 and 17 cm above the LES. The patient was instructed to record in the

diary provided the hours of food intake, changes to supine position and presence of symptoms. The analysis of the study was done with Ohmega software - Ambulatory Impedance-pH Recorder (MMS, NL) and reflux events were detected and classified according to the number of acidic and non-acidic episodes, their composition in liquids, gaseous, mixed and its proximal extension in the esophagus. The reflux episodes were detected by impedance, and 3 categories were established: acids (pH<4); weakly acidic (4≤pH≤7) and non-acidic (pH>7).

Variables measured were distal contraction index (DCI), De Meester index (DMI), acid exposure time (AET), association of symptoms probability (ASP), clearance, peristaltic brakes (PB)), provocation tests: liquid (LPT), viscous (VPT), solid (SPT) and multiple rapid swallow (MRS), presence of HH >4 cm, extra esophageal manifestations (EEM), heartburn and type of (GEJ), and distal latency (DL).

Statistical analysis

For quantitative variables, descriptive statistics arithmetic mean, standard deviation and minimum and maximum values were calculated. For qualitative variables and quantitative variables categorized dichotomously, absolute and relative frequency distributions were calculated. Ouantitative variables were categorized according to their results, whether normal or pathological, or according to the presence or absence of a certain attribute. Additionally, these results were classified according to the group (NERD and volunteers), in order to obtain the corresponding contingency tables, the chi-square independence test (χ^2) was applied to the latter to verify if the variables were associated with the study group, the odds ratios (OR) and their corresponding 95% confidence intervals (CI^{95%}) were also calculated to characterize the statistically significant associations detected.

In order to identify which variables contribute more information to the phenomenon studied, the principal component and multiple correspondence analyzes were applied. In addition, the graphs of scores for the individuals and the graphs of the variables for the analysis of principal components, and the bi-plot graphs for the analysis of multiple correspondences were constructed.

Level of significance was set at 5%, hence a result was considered statistically significant if $p \le 0.05$. Data was processed using the statistical software Minitab 18.0 and Statistical package for social sciences (SPSS) 25.0.

RESULTS

HH length ranged between 1.4 and 6 cm, mean= 2.87 ± 0.78 cm, DL values between 3.6 and 10.1 s, mean= 6.15 ± 1.53 s, non-acid refluxes varied between 0 and 576 refluxes/24-hours, mean= 15.22 ± 59.87 refluxes/24-hours, also, weakly

acid refluxes varied between 0 and 405 refluxes/24-hours, mean=51.58±58.51 reflux/24-hour. Table 1 shows the absolute and relative frequency distributions for qualitative variables and functional tests results presented dichotomously. Most of the variables considered presented a higher percentage of pathological or non-normal results, except for DMI, AET and ASP, also, the type III GEJ and HH<4 cm predominated, in addition, the sample had more female patients.

Table 1: Absolute and relative frequency distributions. All patients.

Variable	Categories	Absolute Frequency	Relative Frequency (%)
Group	Volunteers	20	19
	NERD	85	81
Sex	Female	61	58.1
	Male	44	41.9
DCI	Normal	38	36.2
	Pathological	67	63.8
DMI	Normal	71	67.6
DIVII	Pathological	34	32.4
AET	Normal	65	61.9
ALI	Pathological	40	38.1
ASP	Normal	64	61
	Pathological	41	39
Clearance	Normal	49	46.7
Clearance	Pathological	56	53.3
P.J	Normal	30	28.6
1 J	Pathological	75	71.4
LPT	Physiological	46	43.8
LPI	Paradoxical	59	56.2
VPT	Physiological	31	29.5
VI I	Paradoxical	74	70.5
SPT	Physiological	31	29.5
51 1	Paradoxical	74	70.5
MDT	Physiological	16	24.2
MIDI	Paradoxical	50	75.8
HH > 4 cm	Yes	8	7.6
1111 / 4 CIII	No	97	92.4
EEM	Yes	84	80
EEWI	No	21	20
Heartburn	Yes	83	79
Heartburn	No	22	21
CE I tyme	II	13	12.4
GEJ type	III	92	87.6

NERD: non-erosive gastroesophageal reflux disease. DCI: distal contraction index. DMI: De Meester index. AET: acid exposure time. ASP: association of symptoms probability. PJ: peristaltic jumps. LPT: liquid provocation test. VPT: viscous provocation test. SPT: solid provocation test. MDT: multiple dink test. HH: hiatal hernia. EE: extra esophageal manifestations. GEJ: gastro esophageal junction.

Table 2: Absolute and relative frequency distributions classified by groups.

Variable	Categories	Group (%)		2	OD	CI (OD)	
		NERD	Volunteers	χ^2	OR	CI _{95%} (OR)	p
Sex	Female	50 (82)	11 (18)	0.10	1.17	0.44 - 3.12	0.804
	Male	35 (79.5)	9 (20.5)	0.10	1.1/		
DCI	Pathological	61 (91)	6 (9)	12.22	5.02	2.04 – 17.23	0.001*
	Normal	24 (63.2)	14 (36.8)	12.23	5.93		
DMI	Pathological	31 (91.2)	3 (8.8)	2.41	2.25	0.00 11.00	0.109
	Normal	54 (76.1)	17 (23.9)	3.41	3.35	0.88 - 11.99	
AET	Pathological	36 (90)	4 (10)	2.42	2.04	0.01 0.54	0.077
	Normal	49 (75.4)	16 (24.6)	3.43	2.94	0.91 - 9.54	0.077
ASP	Pathological	38 (92.7)	3 (7.3)	c 00	4.50	1.07 1.01	0.020*
	Normal	47 (73.4)	17 (26.6)	6.00	4.58	1.25 - 16.81	
Clearance	Pathological	50 (89.3)	6 (10.7)	5 41	2.22	1.17 – 9.52	0.026*
	Normal	35 (71.4)	14 (28.6)	5.41	3.33		
PJ	Pathological	70 (93.3)	5 (6.7)	26.10	14.00	4.41 – 44.46	<0.001*
	Normal	15 (50)	15 (50)	26.10	14.00		
LPT	Paradoxical	59 (100)	0 (0)	21.60	_	-	<0.001*
	Physiological	26 (56.5)	20 (43.5)	31.69	∞		
VPT	Paradoxical	69 (93.2)	5 (6.8)	24.56	12.04	4.10 – 40.82	<0.001*
	Physiological	16 (51.6)	15 (48.4)	24.56	12.94		
SPT	Paradoxical	72 (97.3)	2 (2.7)	42.42	40.05	10.31 – 241	<0.001*
	Physiological	13 (41.9)	18 (58.1)	43.43	49.85		
MDE	Paradoxical	45 (90)	5 (10)	40.26	125	14.59 – 1249	<0.001*
MDT	Physiological	1 (6.3)	15 (93.8)	40.26	135		
HH > 4 cm	Yes	7 (87.5)	1 (12.5)	0.24	0.24 1.71	0.20 - 14.70	0.702
	No	78 (80.4)	19 (19.6)	0.24			
EEM	Yes	76 (90.5)	8 (9.5)	24.71	12.67	4.09 – 39.23	<0.001*
	No	9 (42.9)	12 (57.1)	24.71	12.07		
Heartburn	Yes	83 (100)	0 (0)	02.21		-	<0.001*
	No	2 (9.1)	20 (90.9)	93.21	∞		
CEI tuno	II	11 (84.6)	2 (15.4)	0.12	1.24	0.27 – 6.58	1.000
GEJ type	III	74 (80.4)	18 (19.6)	0.13	1.34		

(*) Statistically significant association at 5%. Percentages calculated along the rows. The ORs were calculated taking as reference categories the first row and first column of each contingency table. NERD: non-erosive gastroesophageal reflux disease. DCI: distal contraction index. DMI: De Meester index. AET: acid exposure time. ASP: association of symptoms probability. PJ: peristaltic jumps. LPT: liquid provocation test. VPT: viscous provocation test. SPT: solid provocation test. MDT: multiple dink test. HH: hiatal hernia. EE: extra esophageal manifestations. GEJ: gastro esophageal junction.

 χ^2 test indicated statistically significant association (p≤0.05) between the study groups and the variables DCI, ASP, clearance, PJ, LPT, VPT, SPT, MDT, EEM and heartburn; in addition, there was no statistically significant association (p>0.05) between the study groups and the variables sex, DMI, AET, HH>4cm, and GEJ type. Regardless the statistically significant association, all variables presented OR>1, which indicates it was more likely to find a patient with GERD when the result was pathological or paradoxical and when there was presence of EEM and heartburn, however, some variables presented a stronger association with the study groups reflected in their high OR values, these variables included LPT, VPT, SPT, MRS, PB, EEM and DCI. Finally, for DMI and AET, although the pathological results were more frequent in patients with GERD, this trend was not statistically significant (p>0.05) (Table 2).

Principal components and multiple correspondence analysis

MDT was discarded because it was not measured in all the individuals present in the study, in addition, since all the qualitative variables were dichotomous, they were introduced in the form of dummy variables (y=0 for the absence or normal or physiological result, y=1 for the presence or pathological or paradoxical result). This first classification allowed to identify those variables that presented the greatest contribution to explain the variability of the phenomenon, and at the same time, to identify which of them showed redundant or strongly correlated results in order to select those variables that showed the greatest contribution in terms of variance, and at the same time they will present less correlation with each other.

Table 3: Table of distribution of absolute and relative frequencies for the number of variables with pathological results classified by study group.

		Group (%)		- Total
		NERD	Volunteers	Total
No. of variables with positive results	0	0 (0)	7 (35)	7
	1	2 (2.35)	6 (30)	8
	2	4 (4.71)	5 (25)	9
	3	13 (15.29)	2 (10)	15
	4	25 (29.41)	0 (0)	25
	5	21 (24.71)	0 (0)	21
	6	20 (23.53)	0 (0)	20
Total		85 (100)	20 (100)	105

Percentages calculated along the columns.

Table 4: Table of distribution of absolute and relative frequencies for the number of variables with pathological results classified by study group.

		Group (%)		■ Total	
		NERD	Volunteers	Total	
No. of variables with positive results	0	0 (0)	10 (50)	7	
	1	3 (3.53)	8 (40)	8	
	2	10 (11.76)	1 (5)	9	
	3	25 (29.41)	1 (5)	15	
	4	47(55.29)	0 (0)	25	
Total		85 (100)	20 (100)	105	

Percentages calculated along the columns.

Figure 1A shows the factorial plane constituted by the first two principal components and containing 38% of the phenomenon information. It shows that volunteers tend to group towards the second and third quadrant of the plane, that is, towards negative values of the first main component, also, Figure 1B, shows the representation in the factorial plane of the variables, in the it is also observed that the qualitative variable GEJ type and the quantitative variables DL, HH, non-acid reflux and weakly acid showed the smallest vectors, that is, these variables were the ones that provided less information, and for that reason they were discarded; the rest of the variables that provided more information were all dichotomous, within these, some correlation patterns were identified, in that sense, it was observed that the variables AET and DMI presented a very similar behavior to each other because their vectors were very close, this also happened for EEM and ASP, for heartburn, DCI and PJ, and for all provocation tests, clearance did not show a behavior similar to any other variable.

Since the variables that showed the major contribution of information to the phenomenon were all categorized dichotomous, multiple correspondence analysis was chosen, its objective is similar to the principal components analysis: identify patterns of association between variables and discard those redundant or that show little association with study groups.

Figure 2 shows the bi-plot for the first two principal components, which contains 54.4% of the phenomenon information measured in terms of χ^2 inertia, it can be seen that the provocation tests, heartburn, PJ and DCI are close to the categories of NERD and volunteers simultaneously, although the results of pathological ASP and presence of EEM are close to the NERD category, their normal ASP counterpart and negative EEM, are further away from the category of volunteers. A group of similar responses to each other and less related to the groups under study were clearance, AET and DMI. These similarities and differences in the responses, allow us to propose the discarding of some variables: heartburn was selected because it is the symptom that defines the disease, then, from the group of provocation tests, SPT was selected for presenting greater affinity of the three tests with the study groups, likewise, PJ and DCI can be included, of the four variables, EEM, AET, ASP, clearance and DMI, ASP and clearance were selected; as ASP and EEM have a similar affinity for the study groups, either of them can be selected, in this case, ASP was selected because it was evaluated through the pHMCI and among clearance, AET and DMI, clearance was selected because it was a variable that showed little redundancy with the others in the principal component analysis. In summary, although all the variables provided information measured in terms of association and affinity for the categories of the study groups variable, they were selected for their behavior at heartburn, SPT, PJ, DCI, clearance and ASP, which led to again carry out the multiple correspondence analysis considering these variables.

Figure 3 shows the factorial plane for the first two principal components considering the previously selected variables, which contains 62.7% of the phenomenon information measured in terms of χ^2 inertia, it can be observed that for the selected variables proposals, the pathological, paradoxical results and the presence of EEM and heartburn are very similar to the occurrence of patients with NERD, however, the affinity is less strong, and therefore more dispersed, for the identification of volunteers using normal responses, physiological or absence of EEM, except for the variables heartburn and SPT. This result is not surprising, since as it was seen in the independence tests of γ^2 bivariates, although the relative frequency of pathological results was higher in the group with NERD, they also presented high relative frequencies in the group of volunteers, although always lower than those of the group with NERD, and on the other hand, SPT and heartburn tended to be negative in volunteers and positive in patients with NERD more frequently than the other variables.

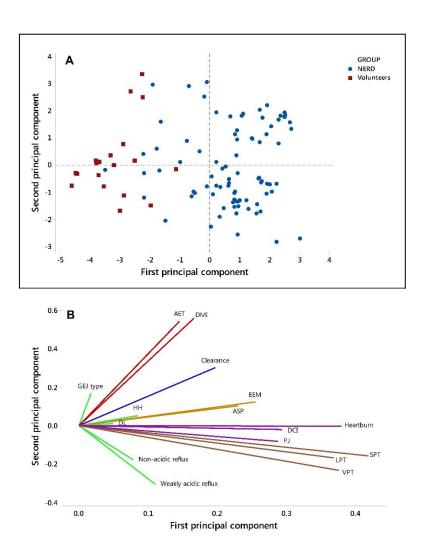


Figure 1: (A) Graph of patient scores in the first two principal components and (B) graph of the vectors of the variables in the first two principal components.

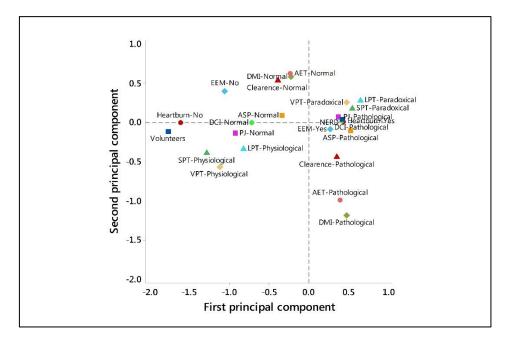


Figure 2: Bi-plot for the categorized variables associated with the study groups.

NERD diagnosis based on selected functional tests

An interesting behavior emerged when we counted how many pathological results and their respective frequencies for the six selected variables (DCI, ASP, clearance, PJ, SPT and heartburn) were presented in the groups under study, Table 3 shows that 79 (79/85; 92.9%) of the patients with NERD did present three or more positive results in the selected variables, while 18 (18/20; 90%) of the volunteers

presented two or less positive results for these same variables, in that sense, if it was established as cut-off to present positive results in three or more of these variables to be declared with NERD, then there would be a criterion of discrimination with 92.9% sensitivity and 90% specificity. It is necessary to indicate that the association between the number of positive results for the six selected variables and the study groups showed statistically significant association (χ^2 =69.62; p<0.001).

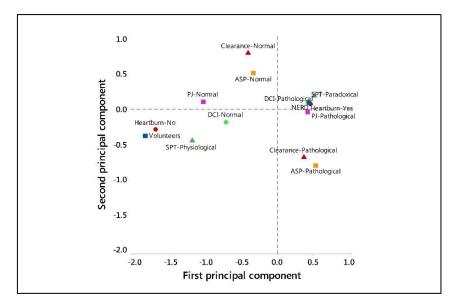


Figure 3: Bi-plot for the categorized variables associated with the study groups. Selected variables.

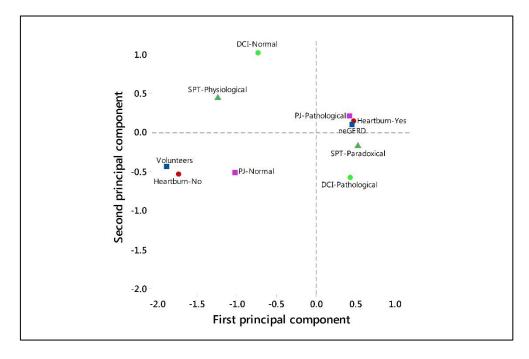


Figure 4: Bi-plot for the categorized variables associated with the study groups. Selected variables deleting ASP and clearance.

On the other hand, it was decided to eliminate clearance and ASP because they are expensive and invasive tests, since they are obtained from the pHMCI study. In this case, the factorial plane of the multiple correspondence analysis (Figure 4) showed a similar behavior to the previous one, only that the affinity of the solids test towards the category

of volunteers seems to be a little lower than that shown by PJ, even so, the general behavior was little affected by the elimination of the variables clearance and ASP.

For the four selected variables (DCI, PJ, SPT and heartburn), Table 4 shows that 82 (82/85; 96.47%) of patients with NERD did have two or more positive results in the selected variables, while that 18 (18/20; 90%) of the volunteers presented one or no positive results for these same variables, in that sense, if it was established as cut-off to present positive results in two or more of these variables to be declared with NERD, then there would be a discrimination criterion with 96.47% sensitivity and 90% specificity.

Likewise, the association between the number of positive results for the four selected variables and the study groups presented a statistically significant association ($\chi^2=78.72$; p<0.001).

This proposal does not rule out the selection of another possible group of variables, (using, for example, EEM instead of ASP and LPT or VPT instead of SPT, or selecting only one of the DCI or PJ variables), since as seen in Figures 1B and 2, the variables tend to be grouped according to their degree of similarity or association, in that sense, these results confirm the complex, multifactorial and multivariate nature of NERD, and at the same time show that it is possible to model their behavior and diagnosis jointly identifying those variables that have a greater impact on their diagnosis.

DISCUSSION

The complexity of NERD is given by diverse symptoms, variable response to drug treatment, multifactorial and heterogeneous pathogenesis and phenotypes strongly influenced by hypersensitivity and hypervigilance. These characteristics are a challenge to establish a simple diagnostic algorithm or categorical classification.²¹

The physiopathology of GERD includes the combination of incompetence of the anti-reflux barrier and motor dysfunction of the esophageal body expressed in incomplete clearance of the refluxed gastric content. The role of weak esophageal peristalsis in the physiopathology of GERD is still under debate, it is not clear whether preexisting motor abnormalities initiate GERD, or if the presence of reflux promotes motor abnormalities of the esophageal body. Several studies have shown that esophageal hypo contractility disorders are associated with delayed bolus transit, both in symptomatic patients and in healthy subjects.²² Conversely, ineffective esophageal motility and presence of peristaltic jumps are associated with significantly prolonged reflux clearance and increased AET in patients with symptomatic GERD.²³⁻²⁵ Martinucci et al. demonstrated that MDT, the amplitude of peristalsis and AET are inversely correlated in patients with GERD.²⁴

Provocation tests increase the sensitivity of HRM to characterize motor function especially in hypomotility states. The increase in esophageal body contraction after a provocation test is called a peristaltic reserve. MRS involves the rapid ingestion of a volume of water of 100-200 ml in approximately 10 seconds. During rapid swallows, the smooth muscle is hyperpolarized by inhibiting contraction in the esophageal body and relaxing the LES, the final swallowing is followed by a vigorous peristaltic contraction and a post LES contraction. A normal response requires intact inhibitory and excitatory central and peripheral neuronal pathways, together with sufficient muscle reserve to produce a strong peristaltic contraction. 24-26

According to the conclusions of the Lyon in 2018, peristaltic dysfunction is an important pathophysiological event in all GERD phenotypes and is more severe the greater the presence of acid, as in Barret's esophagus and disease erosive, that is, it is related to an increase in AET and the appearance of esophageal and extra esophageal symptoms. ²⁷ One of the objectives of the present study was to evaluate the changes in the pattern and vigor of peristalsis in HRM studies in patients with NERD and estimate which of these variables had the highest incidence or association in prolonged clearance, and therefore predict their outcome and avoid the application of more invasive and expensive tests. Prolonged clearance is considered as the determining or reference variable, and the parameters of the Chicago Classification v3.0 are used. ¹⁸

Our study confirmed what was described in the literature that the pathophysiology and behavior of NERD is, in the first instance, multifactorial and that there are many variables or factors that provide statistically significant information (measured in terms of association with NERD). They could help the diagnosis of NERD, however, there is no gold test for the diagnosis of GERD.²

The most commonly used tests include interrogation of symptoms, treatment with proton pump inhibitors, endoscopy, HRM and 24-hour outpatient monitoring. Some tests may or may not be compatible with the initial diagnosis, since the criteria that define NERD are specific to each test. Combined monitoring of multichannel intraluminal impedance and pH (MII-pH) is considered the most sensitive tool for the evaluation of gastroesophageal reflux in patients with NERD since it can detect all types of reflux (gas, liquid, acid, weakly acid reflux and weakly alkaline), its proximal reach and rule out hypersensitive esophagus or functional heartburn, which may confuse the initial diagnosis of NERD. A recent study by Nian et al with 113 GERD patients documented by pHMCI, confirmed that AET and DMI had abnormal values in just 46.02% and 46.90% of patients with GERD and there were no differences significant between these two parameters to discriminate GERD.²¹ In any case, the reflux monitoring demonstrates the consequence of the pathophysiology of GERD, evident as AET, episodes of reflux, delay in clearance, rather than the mechanism by which they occur.

In the pathophysiology of GERD it is important to know if the contribution of each of the factors is similar or of a different nature, if there are some more important than others, and if possible, without losing diagnostic power, select those variables or factors that concentrate the greatest amount of useful information for the diagnosis of NERD.

CONCLUSION

In conclusion, this work provided important elements for the diagnosis of NERD. It is necessary to resort to HRM tool in patients with symptoms of heartburn or EEM, without erosion at endoscopy and without satisfactory response to treatment with proton pump inhibitors. In the presence of two or more of the following alterations: heartburn, DCI<450 mmHg/cm/s in more than 50% of drinks, PS>5 cm in more than 50% of drinks and response paradoxical SPT, they give a criterion of determination of 96.47% sensitivity and 90% specificity for delay of clearance, considering prolonged clearance as the most important pathophysiological variable in NERD, since it is an expression of the motor disorder of the body esophageal, of the incompetence of the barrier and explains in many cases the presence or absence of symptomatology, since a very prolonged clearance allows the prolonged contact of the refluxed material (acidic or non-acidic) and mucosal damage; likewise, the methodology outlined in this work allowed the establishment of an expedited and economic rapid check diagnostic criterion, with good specificity and sensitivity, based on the application of multivariate statistical techniques, in addition, this criterion is flexible due to the multifactorial characteristics of NERD, since the rest of the existing tests or the diagnostic criteria of the attending physician are not categorically excluded, but they serve as a first impression of the general condition of the patient who could potentially suffer from NERD.

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