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Novel impedance-pH parameters are associated with proton pump inhibitor response in patients with inconclusive diagnosis of gastro-oesophageal reflux disease according to Lyon Consensus

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Summary

Background: The Lyon Consensus delineates impedance-pH parameters that can demonstrate/exclude gastro-oesophageal reflux disease (GERD). In patients with acid exposure time between 4% and 6%, GERD diagnosis has been considered inconclusive. In these cases, mean nocturnal baseline impedance (MNBI) and post-reflux swallow-induced peristaltic wave (PSPW) index may either confirm or refute GERD diagnosis and represent predictors of proton pump inhibitor (PPI) response.

Aims: To investigate the diagnostic yield of MNBI and PSPW index and their relationship with PPI response in patients with inconclusive GERD diagnosis.

Methods: Review of impedance-pH tracings from PPI responder/non-responder patients with typical reflux symptoms. Multivariate regression analysis was performed to determine the association of MNBI and PSPW index to PPI response.

Results: Among 233 patients evaluated, 145/233 (62.2%) were PPI responders; 62 had conclusive and 65 inconclusive evidence of GERD, 46 had reflux hypersensitivity, and 60 functional heartburn. Abnormal MNBI and PSPW index were significantly more frequent in inconclusive GERD as compared to the functional heartburn group ($P < 0.001$). Within the inconclusive GERD group, 35/65 (54%) patients were PPI responders and displayed a significantly higher proportion of cases with pathological MNBI or PSPW index as compared to non-responders (32/35 [91.4%] and 30/35 [85.7%] vs 9/30 [30%] and 7/30 [23.3%], $P < 0.001$). By multivariate analysis, pathological PSPW index and/or MNBI values were significantly associated with PPI response in all groups.

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Conclusions: The present study highlights the value of MNBI and PSPW index as adjunctive metrics in characterising patients with inconclusive evidence of GERD and identifying those responsive to PPI treatment.

1 | INTRODUCTION

Gastro-oesophageal reflux disease (GERD) represents one of the most common gastrointestinal disorders, with an increasing worldwide prevalence.[1,2] Clinical manifestations include oesophageal and extra-oesophageal symptoms,[3] whereas GERD can be categorised endoscopically according to the presence of erosive oesophagitis or absence of mucosal injuries.[3] In clinical practice, the diagnosis is mainly based on symptoms and response to empirical trial with proton pump inhibitors (PPIs), whilst in some cases (i.e., partial or absent response to therapy or prior to surgery), a more objective diagnosis is required.[3] The recent Lyon Consensus delineates parameters on ambulatory reflux monitoring that categorically establish and rule out the presence of GERD.[4,5] In particular, conclusive evidence for reflux on oesophageal testing include severe erosive oesophagitis (LA grades C and D), long-segment Barrett's mucosa or peptic strictures on endoscopy or distal oesophageal acid exposure time (AET) >6% on ambulatory pH or multichannel intraluminal impedance-pH monitoring. On the other hand, AET between 4% and 6% is regarded as inconclusive for GERD.[4] In these patients, adjunctive investigative modalities and metrics,[6-12] including high-resolution manometry and novel impedance-pH metrics, may either confirm or refute the diagnosis of GERD.

It has recently been demonstrated that impairment of oesophageal mucosal integrity as shown by low mean nocturnal baseline impedance (MNBI) increases the diagnostic yield of impedance-pH in patients with indefinite GERD and is able to identify patients with borderline AET who respond to anti-reflux therapy.[13] In particular, Patel et al. have demonstrated that distal oesophageal MNBI negatively correlates with AET and, when assessed off-PPI therapy, independently predict symptomatic improvement following anti-reflux medical or surgical treatment.[14] In addition, recent studies exploring the mechanisms underlying oesophageal chemical clearance by means of the post-reflux swallow-induced peristaltic wave (PSPW) index demonstrated that patients with GERD present lower values as compared to controls, being this variable also a potential diagnostic tool when other impedance-pH parameters are inconclusive.[15,16] Moreover, PSPW index appears to be a promising variable in predicting response to acid-suppressive therapy when evaluated both off- or on-PPI therapy.[17-19]

Nowadays, few data on MNBI and PSPW are available in patients with AET between 4% and 6%, i.e., those with indefinite diagnosis of GERD. Moreover, the relationship between these novel impedance-pH parameters and PPI response has not yet been fully investigated in this subgroup of subjects with GERD suspicion. Therefore, we aimed to investigate the diagnostic yield of novel impedance-pH variables and their relationship with PPI response in patients with indefinite diagnosis of GERD.

2 | MATERIALS AND METHODS

2.1 | Patients

Ambulatory 24-hour impedance-pH tracings from consecutive adult patients (age >18 years), assessed at four centres in Italy, were retrospectively evaluated. Inclusion criteria were the presence of dominant oesophageal symptoms (heartburn, regurgitation and non-cardiac chest pain)[20] unresponsive to acid suppressive therapy or responsive but requiring reflux testing to confirm the need for long-term PPI therapy or to document pathologic reflux prior to anti-reflux surgery. A validated structured questionnaire, administered by a senior investigator and based on a four-grade Likert-type scale, was used in each centre to evaluate oesophageal, dyspeptic as well as extra-oesophageal reflux symptoms, (0 = none; 1 = mild/occasional; 2 = moderate/frequent; 3 = severe/constant).[21] Symptoms were considered as troublesome when a score ≥2 was achieved. Further inclusion criteria were age >18 years, and the execution of ambulatory impedance-pH monitoring off acid-suppressive therapy (after at least 7 days of pharmacological wash-out).[22] Tracings considered technically inadequate (i.e., equipment malfunction, poor study quality and presence of artefacts), and patients with evidence of connective tissue disease, psychiatric disease, history of neoplasia and prior foregut surgery were excluded. Impedance-pH studies were always preceded by conventional or oesophageal high-resolution manometry for accurate location of the lower oesophageal sphincter and exclusion of major motility disorders. All patients were treated, within the previous year, with at least 8 weeks of standard dose PPI therapy (esomeprazole 40 mg once daily [od], pantoprazole 40 mg od, lansoprazole 30 mg od and omeprazole 20 mg od). Patients were categorised as non-responders if symptom improvement was <50%.[23,24] Patients with a poor compliance (frequency and timing) to PPI treatment were excluded.

The study was carried out in accordance with the Declaration of Helsinki and was approved by institutional review boards. Signed informed consent was obtained from all individuals before undergoing clinical investigations.

2.2 | 24-hour impedance-pH monitoring

Impedance-pH was recorded using a 2.3-mm diameter polyvinyl catheter assembly containing a series of impedance electrodes, each 4 mm in axial length, spaced at 2-cm intervals, and a distal antimony pH electrode (Sandhill Scientific Inc.). The pH electrodes were calibrated using pH 4.0 and pH 7.0 buffer solutions before impedance-pH monitoring. Following oesophageal manometry, the catheter was passed through

the anaesthetised nostril, and positioned with the pH electrode 5 cm above the lower oesophageal sphincter, and impedance electrodes at 3, 5, 7, 9, 15 and 17 cm proximal to the lower oesophageal sphincter. Impedance-pH was always preceded by conventional manometry or HRM for accurate location of the lower oesophageal sphincter.[25,26]

Event markers, corroborated with paper diaries, were used to record symptoms, meal times and supine periods. Tracings were manually assessed with the aid of commercial software.[27,28] Meal times were carefully identified and excluded. A reflux episode was identified by a 50% decrease in impedance lasting for at least 4 seconds each in distal 2 impedance channels with retrograde propagation.[28] Liquid and liquid-gas reflux events were distinguished into acid (nadir pH <4.0), weakly acidic (nadir pH between 4.0 and 7.0), and weakly alkaline (nadir pH not below 7.0); meal times were excluded. AET was defined as pathological if the time pH <4 exceeded 6% of the total recording time.[4] Reflux-symptom association was assessed using symptom index (SI) or symptom association probability (SAP) for all reflux episodes.[26]

According to impedance-pH findings, patients with AET >6% were defined as having conclusive GERD.[4] Patients with AET between 4% and 6% and with a negative SI/SAP were categorised into the inconclusive GERD group.[4] Patients with AET ≤6% but with a positive SI/SAP were diagnosed as reflux hypersensitivity.[4] All PPI non-responders with AET <4% and without positive SI/SAP were classified as functional heartburn.[4]

MNBI was calculated by measuring baseline impedance values at 3 cm above lower oesophageal sphincter, across stable nocturnal 10-minute periods (at or around 1:00 AM, 2:00 AM and 3:00 AM); the values from the three time periods for both levels were averaged to yield the MNBI for each channel. Values <2292 Ohms (Ω) defined abnormal studies.[16] PSPWs were defined as antegrade 50% drops in impedance in the distal-most impedance channel, with the PSPW starting point must be within 30 seconds after impedance returns to baseline in the distal-most impedance channel after a reflux episode.[15,28] PSPW starting point was considered within 30 seconds after impedance returns to baseline in the distal-most impedance channel after a reflux episode.[28] PSPW did not need to be seen in all impedance channels as long as a swallow was identified in the most proximal channel. PSPW was evaluated using a 2-min window, using a 3000-Ω impedance scale.[28] The PSPW index was calculated dividing the number of PSPWs by the number of reflux events, 61% being the cut-off considered for this study.[15]

2.3 | Statistical analysis

Data are presented as mean and standard deviation (SD) unless otherwise indicated. Comparisons between groups were made using the chi-square and the one-way ANOVA test when appropriate. The ability of MNBI and PSPW index to separate PPI responsive from PPI refractory patients with inconclusive evidence of reflux was assessed by means of receiver operating characteristic (ROC) analysis with calculation of the area under the curve (AUC). Cut-off value for MNBI and PSPW index to identify those inconclusive patients that respond to PPI were identified. Sensitivity and specificity were therefore calculated for both variables. Multivariate regression models were generated to evaluate the association between MNBI and PSPW and PPI response in all groups. Significance was achieved when the *P* value, as adjusted with Tukey HSD correction for multiple comparisons, was <0.05. Statistical analysis was performed using SPSS 27.0 software (SPSS Inc.).

3 | RESULTS

3.1 | Study population

Between 2017 and 2019, a total of 233 patients (127 female; mean age 46 years, range 21–68 years) with typical oesophageal symptoms fulfilled inclusion criteria and formed the study cohort Table 1). Twelve patients had erosive reflux disease (nine grade C and three grade D according to Los Angeles classification). Hiatal hernia was endoscopically detected in 89 out of 233 patients (38.2%).

TABLE 1 Impedance-pH findings among the patients with typical reflux symptoms categorised according to Lyon Consensus

	Conclusive GERD (n = 62)	Inconclusive GERD (n = 65)	Reflux hypersensitivity (n = 46)	Functional heartburn (n = 60)
AET value (mean ± SD)	9.8% (±2.8%)[a]	4.8% (±0.6%)	3.1% (±1.9%)	2.1% (±1.6%)
Reflux episodes (mean ± SD)	86.1 (±24.5)[b]	72.8 (±18.6)	64.3 (±20.2)	53.3 (±9.7)
SAP/SI (n, %)	48 (73.8%)	0	46 (100%)	0
MNBI (mean ± SD)	1153.3 Ω (±463 Ω)[c]	1776.2 Ω (±776.4 Ω)[d]	2080 Ω (±1099.1 Ω)	2428.7 Ω (±793.6 Ω)
PSPW index (mean ± SD)	35.3% (±15%)[e]	50.1% (±20.8%)[f]	55.1% (±26%)	64.3% (±14.7%)

Note: Data are presented as mean ± SD.

[a]$P < 0.001$ vs inconclusive GERD, reflux hypersensitivity and functional heartburn.

[b]$P < 0.001$ vs inconclusive GERD, reflux hypersensitivity and functional heartburn.

[c]$P < 0.001$ vs inconclusive GERD, reflux hypersensitivity and functional heartburn.

[d]$P < 0.001$ vs reflux hypersensitivity and functional heartburn.

[e]$P < 0.001$ vs inconclusive GERD, reflux hypersensitivity and functional heartburn.

[f]$P < 0.001$ vs functional heartburn.

3.2 | Impedance-pH data in pathological GERD, inconclusive GERD, reflux hypersensitivity and functional heartburn patients

According to impedance-pH, 62 patients were classified as having conclusive GERD. There were 65 patients in the inconclusive GERD group, whilst 46 patients had reflux hypersensitivity and 60 had functional heartburn (Figure 1). Conclusive GERD group demonstrated a significantly higher mean AET value, higher mean number of reflux episodes and lower mean values of MNBI and PSPW index as compared to patients with inconclusive GERD, reflux hypersensitivity and functional heartburn ($P < 0.001$ for all comparisons, Table 1). Inconclusive GERD group displayed significantly lower mean MNBI value when compared to reflux hypersensitivity and functional heartburn patients ($P < 0.001$ for both, Table 1). Moreover, inconclusive GERD group displayed significantly lower mean PSPW index value when compared to functional heartburn patients ($P < 0.001$, Table 1).

Conclusive GERD group presented a significantly higher proportion of cases with abnormally low MNBI and PSPW index values compared to inconclusive GERD, reflux hypersensitivity and functional heartburn group ($P < 0.001$ for each comparison) (Figure 1). Inconclusive GERD and reflux hypersensitivity groups were characterised by a significantly higher proportion of individuals with abnormal MNBI and PSPW index values compared to functional heartburn group ($P < 0.001$ for each comparison) (Figure 1). Among the whole study population, patients presenting only pathological AET and/or positive SAP/SI were 108 out of 233 (46.3%). When considering also MNBI and PSPW index, the proportion of individuals with at least one pathological impedance-pH variable was 176 out of 233 patients (75.5%) ($P < 0.001$).

3.3 | Impedance-pH, endoscopic findings and PPI response

A total of 145 out of 233 patients were responders to PPI therapy (62.2%). Responder and non-responder groups were characterised by similar proportion of patients showing hiatal hernia (34.5% vs 44.3%, P = ns) and/or erosive esophagitis at upper endoscopy (5.5% vs 4.5%, P = ns). On the other hand, responder patients were characterised by a significantly higher mean AET value and lower mean MNBI and PSPW index values compared to non-responders, whilst mean reflux number values were comparable between the two groups (Table 2). Responder group presented a significantly higher proportion of individuals with pathological MNBI or PSPW index compared to non-responders (Table 2).

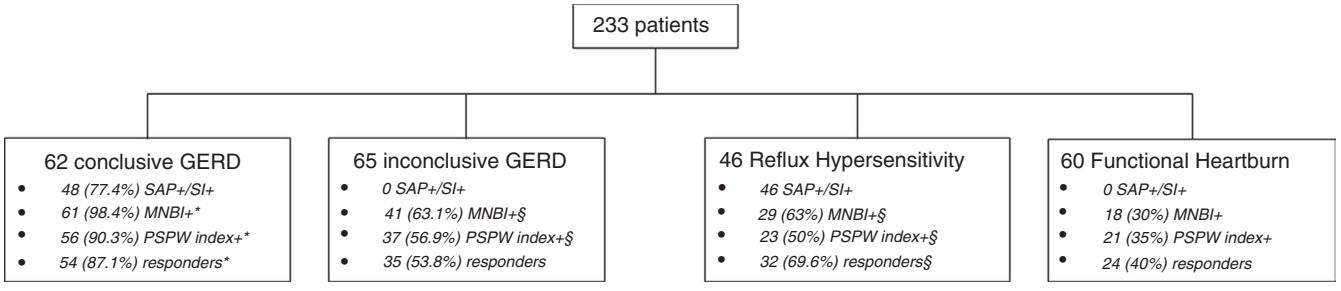
Conclusive GERD group was characterised by a significantly higher proportion of patients responding to PPI compared to inconclusive GERD, reflux hypersensitivity and, as expected functional heartburn groups (Figure 1). Moreover, reflux hypersensitivity group presented a significantly higher frequency of patients responding to PPI compared to functional heartburn group ($P = 0.003$) (Figure 1). In addition, inconclusive GERD group displayed a higher rate of responder patients compared to functional heartburn group, although this difference was not statistically significant ($P = 0.15$) (Figure 1).

Among inconclusive GERD group, 35 patients were responders, and 30 non-responders to PPI. Responders displayed a significantly higher proportion of individuals with pathological MNBI or PSPW index values as compared to non-responders (32 out of 35 [91.4%] and 30 out of 35 [85.7%] vs nine out of 30 [30%] and seven out

TABLE 2 Impedance-pH findings in PPI responders and non-responders

	Responders (n = 145)	Non-responders (n = 88)
AET value (mean ± SD)	5.8% (±3.5%)[a]	4% (±3.3%)
Reflux episodes (mean ± SD)	72.9 (±23.7)	64.4 (±19)
MNBI (mean ± SD)	1545.6Ω° (±826Ω)[a]	2385.9Ω (±825.5 Ω)
PSPW index (mean ± SD)	42.3% (±20%)[a]	66.3% (±16.5%)
% pathological MNBI	119 (82.1%)[a]	30 (34.1%)
% pathological PSPW index	115 (79.3%)[a]	22 (25%)

Note: Data are presented as mean ± SD.
[a]$P < 0.001$ vs. non-responders.



*p <0.01 vs inconclusive GERD, reflux hypersensitivity and functional heartburn patients
§p <0.01 vs functional heartburn patients

FIGURE 1 Flow diagram of patients according to impedance-pH parameters and proportions of responders to PPIs

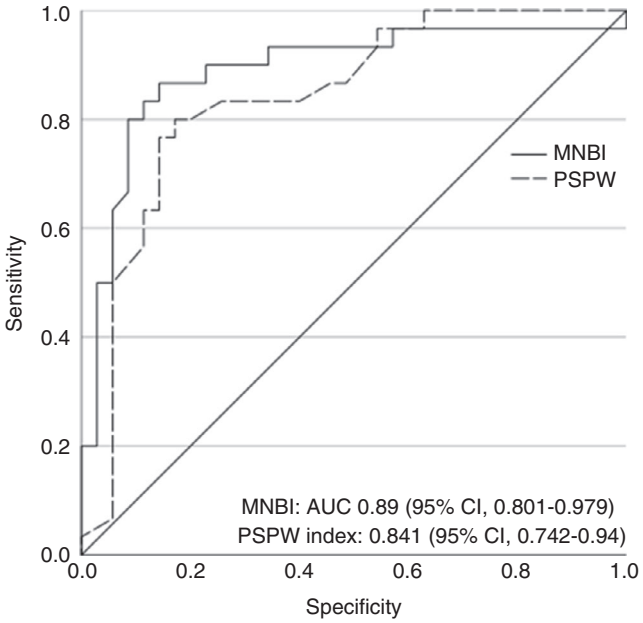


FIGURE 2 ROC curves and AUC values (95% confidence intervals, CIs) of MNBI and PSPW index in inconclusive GERD patients

TABLE 3 Multivariate logistic regression analysis of association between MNBI, PSPW index and PPI response in patient groups

	MNBI		PSPW index	
	Odds ratio (95% CI)	*P* value	Odds ratio (95% CI)	*P* value
Conclusive GERD	2.1 (1.4-2.8)	<0.001	2.3 (1.5-3.2)	<0.001
Inconclusive GERD	2.4 (1.5-3.1)	<0.001	2.2 (1.3-2.7)	<0.001
Reflux hypersensitivity	1.9 (1.2-2.7)	<0.01	1.8 (1.1-2.6)	<0.01
Functional heartburn	2.3 (1.7-3.0)	<0.001	2.1 (1.2-2.9)	<0.01

of 30 [23.3%], $P < 0.001$ for both comparisons). At ROC analysis, both PSPW index and MNBI were significantly associated to PPI responsiveness in the inconclusive GERD group (Figure 2). A MNBI cut-off of 1916 Ω and a PSPW index cut-off of 52% were identified to discriminate responders from non-responders among inconclusive GERD patients, both displaying a sensitivity of 80% whilst the specificity was 91.4% and 82.9%, respectively.

According to multivariate analysis, the presence of pathological MNBI or PSPW index values was significantly associated with PPI response in all groups (Table 3).

4 | DISCUSSION

The present study was aimed at investigating the diagnostic yield of novel impedance-pH variables in either confirming or refuting the diagnosis of GERD in patients with an oesophageal acid exposure between 4% and 6% and evaluating their relationship with PPI response in these subjects with an inconclusive diagnosis of GERD according to Lyon Consensus criteria. Normative values for these parameters have been proposed in pilot investigations[15-17] but are still awaiting generalised validation since consensus rules for assessment of impedance-pH tracings have only recently been defined[28] and provisional data are currently available.[29]

In agreement with several previous investigations,[13-19] we confirm that MNBI and PSPW index can increase the diagnostic yield of impedance-pH in patients with typical reflux syndrome. In particular, more than half of patients belonging to the inconclusive GERD were characterised by evidence of reflux disease at impedance-pH, as confirmed by pathological MNBI and/or PSPW index values. We also investigated the potential link between MNBI, PSPW index and PPI response in our study cohort. The PPI responder group was characterised by a significantly higher proportion of individuals with pathological MNBI or PSPW index compared to non-responders. At ROC analysis, both PSPW index and MNBI were significantly associated to PPI responsiveness in the inconclusive GERD group. We have identified a MNBI cut-off of 1916 Ω and a PSPW index cut-off of 52%, accurately discriminating responders from non-responders among inconclusive GERD patients, as confirmed by a sensitivity of 80% for both and a specificity of 91.4% and 82.9%, respectively. These values are actually close to the values proposed from the above mentioned studies, thus confirming their accuracy in discriminating patients with reflux disease as well as their usefulness in predicting PPI response. The multivariate analysis showed that pathological MNBI or PSPW index values were significantly associated with PPI responsiveness in all groups. These findings are in agreement with previously published data showing the usefulness of these metrics in identifying true GORD patients and predict response to therapy.[17,19,30] In addition, it has been recently shown that PSPW-associated changes of pH value can efficiently predict PPI response in patients undergoing off-therapy impedance-pH monitoring.[18] Thus, we may speculate that PSPW index is associated with PPI responsiveness since it is able to discriminate those patients likely being affected by true reflux disease as well as reflecting the effectiveness of the volume and chemical clearing in them.

To the best of our knowledge, this is the first investigation demonstrating that the majority of patients with inconclusive GERD diagnosis, as defined according to the Lyon Consensus, display evidence of reflux disease according to the novel impedance-pH variables. Moreover, according to our results, 35 out of 65 (53.8%) inconclusive GERD patients show a satisfactory response to previous proper PPI treatments, having a significantly higher rate of pathological MNBI or PSPW index values as compared to non-responders. Our results demonstrate that more than half of patients with inconclusive GERD diagnosis are characterised by both presence of pathological MNBI and/or PSPW index values and PPI responsiveness and, hence, can be considered as affected by proven GERD. The only currently available study focusing on this subgroup of GERD patients demonstrated that, when low, MNBI identifies patients with borderline AET who respond to anti-reflux therapy.[13] Our results are in agreement with those from the above-mentioned investigation,

and PSPW index data further corroborate the hypothesis that these novel impedance-pH parameters are able to discriminate true GERD patients and predict response to acid-suppressive therapy.

It has been previously demonstrated that baseline impedance inversely correlates with AET, directly relates to ultrastructural changes in the oesophageal epithelium and could be responsible for perception of heartburn.[31-33] The PSPW index assesses efficacy of oesophageal chemical clearance, an important defence mechanism against reflux elicited by a vagal oesophago-salivary reflex and delivering salivary bicarbonate[15] into the distal oesophagus. Conceivably, a reduced clearance capability may contribute to increased paracellular permeability allowing a prolonged contact of oesophageal epithelium with reflux components, and, therefore, favouring the occurrence of ultrastructural mucosal damage as shown by low values of MNBI.

Results reported herewith may raise the question if the AET cut-off values proposed by the Lyon Consensus are actually able to discriminate patients with true GERD, in particular in patients with indefinite diagnosis. Indeed, our findings may suggest that the grey area of patients with AET values between 4% and 6% encompasses a considerable group of patients to be regarded as proven GERD. It could be argued that the proposed AET cut-off >6% may be too specific, given that the majority of patients with inconclusive GERD diagnosis have pathological MNBI and/or PSPW index values. On the other hand, it is also tempting to hypothesise that the current MNBI and PSPW index thresholds may be too sensitive, given one third of non-responders have pathological MNBI and/or PSPW index values. Nevertheless our results, although not definitively solving this dilemma, actually show that MNBI and PSPW index are useful tools in patients with inconclusive GERD, being independently associated with satisfactory PPI response and, therefore, probably unveiling an unclear diagnosis of reflux disease in these patients. Future prospective multicentre outcome studies evaluating shared threshold of impedance-pH variables may elucidate the role of impedance-pH variables in confirming GERD diagnosis and predicting outcome with medical or surgical therapy.

As far as we know, this is the first study aimed at evaluating the potential factors associated with PPI response in patients with inconclusive GERD diagnosis. Efforts were made to identify a large cohort of patients presenting with dominant typical oesophageal symptoms and evaluated with impedance-pH monitoring. We selected patient responder or not responder to PPI therapy, who needed documentation of abnormal reflux burden prior to long-term PPI therapy or to anti-reflux surgery. Our enrolment criteria reflect clinical practice, contemplating a preliminary management with a PPI trial. Some limitations could temper the strengths of our investigation. In particular, the retrospective nature of the study, although data collection was prospectively carried out for the whole study population. Moreover, impedance-pH tracings were evaluated separately in each centre involved in the study, although a satisfactory agreement between the same investigators has been achieved in previously published studies based on impedance-pH tracings analysis.[10,11,18,34,35] Finally, the day-to-day variability of reflux testing and the placebo effect may have underestimated the number of patients with GERD and may have overestimated number of responders, respectively, particularly in patients without evidence of reflux disease.[21]

In conclusion, the present study highlights the effectiveness of MNBI and PSPW index in increasing the diagnostic yield of impedance-pH and in identifying patients with inconclusive GERD responsive to PPI therapy.

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Author contributions: MR, MF, EM, ES and MC: Study concept and design; collection, analysis and interpretation of data; drafting of the manuscript. GDC, SZ, DM and PB: collection, analysis and interpretation of data.

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