On-therapy impedance-pH monitoring can efficiently characterize PPI-refractory GERD and support treatment escalation.

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Abstract

Background: On-therapy impedance- pH monitoring is recommended in patients with documented GERD and PPI-refractory heartburn in order to establish whether the unremitting symptom is reflux-related or not.
Aims: To define on-PPI cut-offs of impedance-pH metrics allowing proper interpretation of on-therapy impedance-pH monitoring.
Methods: Blinded expert review of impedance- pH tracings performed during double-dosage PPI, prospectively collected from 150 GERD patients with PPI-refractory heartburn and 45 GERD patients with PPI-responsive heartburn but persisting extra-esophageal symptoms. Acid exposure time (AET), number of total refluxes (TRs), post- reflux swallow-induced peristaltic wave (PSPW) index, and mean nocturnal baseline impedance (MNBI) were assessed. On-PPI cut- offs were defined and evaluated with ROC analysis and the area under curve (AUC).
Results: All the four impedance- pH metrics significantly differed between PPI- refractory and PPI- responsive heartburn cases. At ROC analysis, AUC was 0.73 for AET, 0.75 for TRs, 0.81 for PSPW index, and 0.71 for MNBI; best cut- offs were ≥1.7% for AET, ≥45 for TRs, ≤36% for PSPW index, and ≤ 1847 Ω for MNBI; AUC of such cut- offs was 0.66, 0.71, 0.73, and 0.68, respectively. Analysis of PSPW index and MNBI added to assessment of AET and TRs significantly increased the yield of on- therapy impedance- pH monitoring in the PPI- refractory cohort (97% vs. 83%, p< 0.0001). Notably, suboptimal acid suppression as shown by AET ≥1.7% was detected in 43% of 150 PPI-refractory cases.
Conclusions: We have defined on-PPI cut-offs of impedance-pH metrics by which comprehensive assessment of impedance- pH tracings, including analysis of PSPW index and MNBI can efficiently characterize PPI- refractory GERD and support treat -ment escalation.

KEYWORDSGERD, impedance-pH monitoring, MNBI, PPI, PSPW index, refractory GERD

1 | INTRODUCTION

Gastro-esophageal reflux disease (GERD) develops when the reflux of stomach contents causes troublesome symptoms and/or mucosal damage, heartburn representing the most sensitive, specific, and reliable GERD symptom.(1,2) The pathogenesis of GERD is multifactorial, including incompetence of the gastro-esophageal junction, impaired esophageal clearance of refluxate, and damaging action of refluxed gastric contents.(3) Acid reflux is regarded as the major pathogenic factor in GERD: indeed, acid suppression by proton pump inhibitor (PPI) therapy is the keystone of medical treatment, allowing healing of reflux esophagitis and suppression of heartburn in most cases, so that remission of the symptom following a PPI trial is considered sufficient to confirm its relationship with reflux in clinical practice.(4) Uninvestigated patients with PPI-responsive heartburn often become PPI-dependent, and objective confirmation of GERD is required to confirm indication for long-term PPI management or for antireflux surgery. Conversely, several patients complain of per-sistent troublesome heartburn despite double-dosage PPI treatment: they require careful investigation to objectively establish whether they have GERD, and then whether on-PPI unremitting heartburn is reflux-related or reflux-unrelated.(5-7) In such clinical settings, upper GI endoscopy is most often negative and reflux monitoring is warranted.(5-7) A hierarchical approach to GERD diagnosis by means of reflux monitoring has been proposed by the Lyon Consensus,(8) based on shared thresholds for acid exposure time (AET): AET has been regarded as physiological when <4% and definitely pathological when >6%, whereas intermediate values have been defined inconclusive and requiring assessment of supportive parameters, that is, number of reflux episodes, symptom-reflux association indexes, and new metrics, namely post-reflux swallow-induced peristaltic wave (PSPW) index and mean nocturnal baseline impedance (MNBI).(8) The clinical value of such a hierarchical approach has been validated in a recent study comparing 488 PPI-dependent endoscopy-negative heartburn cases with 70 healthy controls(9) and in a study evaluating 317 patients with endoscopy-negative PPI- refractory heartburn(10); in both studies, manual analysis of off-therapy impedance-pH tracings was carried out with adherence to meticulous rules established in a recent expert consensus.(11) These studies allowed us to confirm the clinical value of the physiological thresholds of AET (4%) and TRs (40) as proposed by the Lyon Consensus, and of the updated physio -logical thresholds of PSPW index (50%) and MNBI (2000 Ω).(9,10)
In patients with proven GERD, on- PPI impedance-pH monitoring is currently advocated to objectively ascertain whether unremitting symptoms are reflux-related, thus defining PPI-refractory GERD and supporting treatment escalation including surgery.(5-8,12,13) However, it has been shown that double-dosage PPI therapy reduces AET in both PPI-responsive and PPI-refractory GERD,(14) and in healthy subjects too.(15,16) Moreover, impedance metrics are modified by double-dosage PPIs,(14) making off-therapy thresholds of conventional and new impedance-pH metrics suboptimal for on-therapy testing. Our aims were to define on-PPI cut-offs of impedance-pH metrics characterizing PPI-refractory GERD, and to evaluate their clinical value. For these purposes, we compared on-therapy impedance-pH tracings from GERD patients with PPI-refractory heartburn with those from GERD patients with PPI-responsive heartburn but persisting extra-esophageal symptoms.

2 | MATERIALS AND METHODS

The study consisted of blinded review of on-therapy impedance-pH tracings from patients with proven GERD, prospectively evaluated at an Italian referral center for troublesome PPI-refractory heartburn or for PPI-responsive heartburn with persistent troublesome extra-esophageal

symptoms. The study was carried out in accordance with the Declaration of Helsinki; since investigations were carried out for clinical reasons only, according to Italian law formal medical ethical assessment was not required. Signed informed consent was warranted before any clinical investigation. GERD was previously documented on the basis of erosive reflux disease detected at upper GI endoscopy (grade B- C- D reflux esophagitis according to Los Angeles score),(5) or AET >4%(17) at off-therapy pH-monitoring or impedance-pH monitoring in accordance with normative values established in healthy subjects eating a Mediterranean diet,(18) a cut-off coinciding with the normal AET value proposed by the Lyon Consensus.(8) Esophageal and extra-esophageal symptoms (cough, wheezing, hoarseness, throat clearing) were assessed by means of a validated structured questionnaire,(19, 20) consisting of a four-grade Likert-type scale scoring system administered by a senior gastroenterologist. Briefly, scores were as follows: 0, none; 1, mild/occasional; 2, moderate/frequent; 3, severe/constant, and were considered troublesome for score 2 or 3. The PPI-refractory heartburn cohort was defined by off-therapy troublesome heartburn (score 2 or 3) persisting after at least 8-week twice-daily PPI taken 30–60 min before breakfast and before dinner (packages returned at follow-up visit for pill count). The PPI-responsive heartburn cohort was defined by off-therapy troublesome heartburn (score 2 or 3) suppressed (score 0 or 1) by label-dose PPI but associated with troublesome extra-esophageal symptoms persisting despite at least 8-week twice-daily PPI. Previous esophago-gastric surgery, Sjogren syndrome, progressive systemic sclerosis, psychiatric disorders, and Barrett's esophagus constituted exclusion criteria. Impedance-pH monitoring was performed during double-dosage PPI therapy started from at least 8 weeks and using the Diversatek/Sandhill equipment (Diversatek Healthcare, USA); it was always preceded by conventional or high-resolution esophageal manometry in order to accurately locate the lower esophageal sphincter (LES) and exclude major motility disorders.(7,17) The impedance-pH probe (ComforTECZAN BG-44®, Diversatek Healthcare, USA) allowed monitoring impedance values at 3, 5, 7, 9, 15, and 17 cm above the upper LES border, and pH values at 5 cm above and 10 cm below the upper LES border. For the purposes of the present study, impedance-pH tracings were reviewed by one expert investigator (MF) blinded to the clinical setting (PPI-refractory or PPI- responsive heartburn). Tracings were analyzed following the Wingate Consensus criteria11 with the aid of the Bioview® software (Diversatek/Sandhill, USA). Two-min time windows were assessed, with zooming whenever deemed nec -essary and exclusion of meal times. Conventional impedance-pH metrics were assessed, including AET, number of acid, weakly acidic and total refluxes (TRs), and percentage gastric acid exposure time; positive heartburn-reflux association was defined by combined positivity of symptom association probability (SAP) and symptom index (SI), that is >95% and > 50%, respectively.(8) Esophageal chemical clearance was assessed with the PSPW index: a PSPW was defined as an antegrade 50% drop in impedance, originating in the proximal esophagus within 30s after the end of a reflux event and reaching the distal lumen,11 and the PSPW index was calculated dividing the number of PSPWs by the number of TRs.21 Mucosal integrity was assessed with MNBI: during the night- time recumbent period, the baseline impedance was measured in the most distal impedance channel in three 10-in time periods, selected with avoidance of swallows, refluxes and pH drops below 4.0, and the mean of three measurements was calculated.(22) Criteria for positivity of on-PPI impedance-pH monitoring in PPI-refractory GERD based on receiver operating characteristics (ROC)-defined cut-offs of the four impedance-pH metrics were compared with those based on ROC- defined cut-offs of AET and TRs (0.5% and 40, respectively) as proposed in a recent multicenter study.162.1 | StatisticsContinuous variables are expressed as median and interquartile range (IQR) unless otherwise specified; comparisons were made with the Mann–Whitney U test.

Categorical variables were com -pared using the Fisher's exact test. Correlation between AET and gastric acid exposure time was assessed using Spearman's rank correlation coefficient. ROC analysis with calculation of the area under curve (AUC) and 95% confidence interval (CI) was used to test the efficiency of the four impedance-pH metrics in separatingPPI- refractory from PPI- responsive cases; on- therapy cut- offs were defined by selection of the values that maximized the sum of sensitivity and specificity. The performance of such cut- offs in distinguishing PPI- refractory from PPI- responsive heartburncases was then evaluated with calculation of AUCs, sensitivity, specificity, negative predictive value (NPV), and positive predictive value (PPV). STATA statistical software, release (16) (STATA, College Station, TX) was employed. A $p< 0.05$ was considered significant.

3 | RESULTS

The PPI-refractory heartburn cohort consisted of 150 cases while the PPI- responsive heartburn cohort consisted of 45 cases: baseline characteristics are reported in Table 1. The PPI-refractory heartburn cohort was characterized by higher prevalence of hiatal hernia and erosive reflux disease, higher burden of acid and weakly acidic reflux and lower values of PSPW index and MNBI. At on- PPI impedance-pH monitoring, heartburn was recorded by 76/150 (51%) and 0/45 PPI- refractory and PPI- responsive cases, respectively; combined SAP and SI positivity for heartburn was detected in less than one third of cases in the PPI- refractory cohort. The correlation between AET and gastric acid exposure time was weak both in the PPI- refractory and in the PPI-responsive group, although significant (0.39 and 0.44, respectively, $p< 0.01$); residual gastric acidity did not differ between the two groups. Weakly acidic refluxes were three times more numerous than acid refluxes in the PPI- refractory heartburn cohort, as expected.(14) AET and TRs were significantly higher and PSPW index and MNBI were significantly lower, respectively, in the PPI-refractory group.At ROC analysis, AUCs were good, that is, >0.7 for AET, TRs, and MNBI, and excellent, that is, >0.8 for PSPW index (Figure 1); best cut- offs were ≥1.7% for AET, ≥45 for TRs, ≤36% for PSPW index, and ≤ 1847 Ω for MNBI. Considering such cut- offs, the AUC at ROC analysis was >0.7 for TRs and PSPW index (Figure 2). Positivity of the four impedance-pH metrics applying the ROC- defined cut-offs was significantly more often detected in the PPI- refractory group (Table 2); notably, AET was ≥1.7% was detected in 43% of cases in the PPI-refractory heartburn cohort and in 11% ($p< 0.0001$) of cases in the PPI- responsive heartburn cohort with persisting extra- esophageal symptoms. The performance characteristics of the ROC- defined cut- offs of the four impedance-pH metrics are reported in Table 3, all four metrics showing very high PPV. In the PPI- refractory cohort, the gain afforded by PSPW index and/or MNBI positivity added to AET and/or TRs positivitywas significant (146/150 vs. 124/150, i.e., 97% vs. 83%, $p< 0.0001$)(Figure 3). Criteria for impedance-pH monitoring positivity in the PPI- refractory heartburn cohort applying our on- therapy ROC- defined cut- offs were significantly more efficient than by applyingthe on- therapy cut- offs recently proposed for AET and TRs16 (97% vs. 76%, $p< 0.00001$) (Table 4).

DISCUSSION

In the present study, on- therapy impedance-pH tracings from pa -tients with documented GERD and PPI- refractory or PPI- responsive heartburn were blindly reviewed. We focused on heartburn because it is the most sensitive, specific, reliable, and PPI-

responsive GERD symptom.1,2,4 mpedance-pH monitoring affords a comprehensive assessment of reflux allowing to evaluate acid (AET) and over -all reflux burden (TRs), reaction against reflux (PSPW index) reflux- related esophageal mucosal damage (MNBI). On-therapy trac -ings from PPI- refractory cases were characterized by higher overall reflux burden, less efficient chemical clearance of refluxate, higher esophageal acid exposure, and more severe impairment of mucosal integrity as assessed with TRs, PSPW index, AET, and MNBI, re -spectively. On- PPI cut- offs of the four impedance-pH metrics were defined by means of ROC analysis, affording efficient separation of PPI- refractory from PPI- responsive heartburn cases with high PPV. In the PPI- refractory heartburn group, appraisal of PSPW and MNBI added to assessment of AET and TRs significantly increased the yield of on- therapy impedance-pH monitoring. Of note, in the PPI- refractory heartburn cohort on- PPI AET was higher than the 1.7% ROC-defined cut-off in nearly half of cases.

In the PPI- refractory heartburn cohort, higher prevalence of hiatal hernia and erosive reflux disease was detected. Esophageal mucosal injury is regulated by the duration of exposure and the causticity of refluxate, which are determined by the effectiveness of esophageal reflux clearance, in turn affected by salivation and the presence of a hiatal hernia.3 It has long been recognized that the presence of a hiatal hernia significantly reduces PPI efficacy in diminishing esophageal acid exposure(23) and is associated with high prevalence of reflux esophagitis, detected in up to 88% of cases.(10 ,19-21) In the present study, the PPI-refractory heartburn cohort was characterized by more severe impairment of the anti-reflux bar -rier, as shown by higher prevalence of hiatal hernia, in turn associated with more severe mucosal damage as shown by higher prevalence of erosive reflux disease; in other words, GERD patients with PPI- refractory heartburn were characterized by a more complex, severe, and difficult-to- treat disease as reflected by PPI failure. Our on- PPI impedance-pH findings confirm that ultrastructural esophagealmucosal damage, as shown by low MNBI values, is associated with high overall and acid reflux burden, as documented by high values of TRs and AET, respectively, and with impaired reaction to reflux as demonstrated by low values of PSPW index, in accordance with off- therapy findings. (9,10)

On- therapy impedance-pH monitoring is currently advocated in patients with proven GERD in order to document a direct relationship between PPI- refractory symptoms and reflux,(5-7,12,13) thus providing objective support for escalation of antireflux treatment. In other terms, the aim of on- therapy impedance-pH monitoring in patients with documented GERD is to verify whether reflux is the actual cause of unremitting symptoms despite PPI therapy. In the present study, we compared 150 GERD patients with PPI- refractory heartburn to 45 GERD patients with PPI-responsive heartburn, differently from a recent study comparing PPI-refractory patients with healthy volunteers.16 In that study,16 half of GERD cases were extracted from a clinical trial comparing magnetic sphincter augmentation and medical management; since magnetic sphincter augmentation is contraindicated for hiatal hernia >3 cm, the latter constituted an exclusion criterion for the entire cohort of GERD cases, limiting the clinical applicability of results in PPI- refractory GERD which is characterized by high prevalence of hiatal hernia, often >3 cm.(10,19-21) The 0.5% AET cut- off proposed in the study by Gyawali et al.(16) showed a non-significant (p= 0.22) 0.58 AUC at ROC analysis, a little bit disappointing result probably favored by the decision to compare GERD cases with healthy controls causing oversuppression of physiologic acid reflux in the latter group, in turn affecting ROC analysis and cut-off definition. Considering that lack of symptomatic response to PPI therapy cannot be assessed in healthy volunteers, we reasoned that a cohort of GERD cases with PPI- responsive heartburn could be a more appropriate comparator to a cohort of

GERD cases with PPI- refractory heartburn. On-PPI impedance-pH motoring in GERD patients with PPI-responsive heartburn but PPI-refractory extra-esophageal symptoms has been advised to reveal a relationship, if any of unremitting symptoms with reflux.(5) We therefore choose to compare on-therapy impedance-pH tracings from GERD cases with PPI-refractory heartburn to those from GERD cases with PPI-responsive heartburn investigated for persistent extra-esophageal symptoms because this is the main indication to perform on-PPI impedance-pH monitoring in patients with PPI-responsive heartburn in clinical practice.
In the PPI-refractory heartburn cohort, combined SAP and SI positivity was detected in less than one third of cases, confirming the modest clinical value of these parameters.(9,10) Gastric acid exposure time did not differ between the two groups and showed weak correlation with AET, confirming the limited clinical relevance of this metric.(16) AET, TRs, PSPW-index, and MNBI significantly differed between PPI-refractory and PPI-responsive cases, affording good discriminating performance at ROC analysis, in turn confirmed applying ROC- defined cut-offs. Indeed, the cut-offs defined by ROC analysis of the four metrics provided very high PPV in characterizing the PPI-refractory heartburn cohort. A few patients in the PPI-responsive heartburn cohort had out of range metrics suggesting incomplete suppression of reflux, contrary to the PPI-refractory heartburn cohort in whom nearly all cases showed out-of-range metrics: this finding is possibly related to on-PPI persistent extra-esophageal symptoms in the PPI- responsive heartburn cohort. On-PPI impedance-pH monitoring has long been advocated for establishing a cause-and-effect relationship between reflux and extra-esophageal reflux symptoms,(5) but no test is currently regarded as reliable for such a purpose24: this clinically relevant issue could be solved by future prospective investigations adopting the cut-offs we propose in the present study. Notably, applying ROC-defined cut-offs a significant increment of impedance-pH positivity was found by adding appraisal of PSPW index and MNBI to assessment of AET and TRs in the PPI- refractory heartburn group. Moreover, criteria for impedance-pH monitoring positivity based on the ROC-defined cut-offs of the four impedance-pH metrics were more efficient in characterizing PPI- refractory heartburn cases than criteria based on the AET and TRs cut-offs recently proposed.(16) According to these findings, comprehensive assessment of on-PPI impedance-pH monitoring based not only on AET and TRs but also on PSPW index and MNBI affords significant increment in the proportion of GERD patients with PPI- refractory heartburn in whom objective evidence of ongoing reflux can be detected, thus allowing to more efficiently identify cases in whom benefit from treatment escalation can be predicted. It has been argued that assessment of PSPW index and MNBI requires additional time for analysis of impedance-pH tracings(25): however, given the current limitations of available commercial software for recognition of reflux events, manual analysis of impedance-pH tracings is regularly warranted(6) and the time required is mainly due to meticulous definition of reflux episodes(11) whereas the additional time needed for calculation of PSPW index and MNBI consists of few minutes only, an extra time justified when the issue is a firm diagnosis of PPI-refractory GERD, reliable enough to support treatment escalation including surgery. Interestingly, a recent study suggests that artificial intelligence can afford accurate measurement of reflux episodes and PSPWs, thus favoring wider application of impedance-pH monitoring.(26) Currently, there is wide consensus that antireflux surgery represents a valuable management option for PPI-refractory typical GERD,(4,12,13) provided that patients are regularly offered thorough evaluation including on-PPI impedance-pH monitoring.(27) The on-PPI cut-offs of the four impedance-pH metrics we assessed provided very high PPV in characterizing GERD patients with PPI-refractory heartburn, resulting than suitable for pre-surgical evaluation. Several patients fear of side effects and complications of laparoscopic fundoplication (28) or are unfit for surgery, however. As an alternative to surgical interventions, baclofen can

represent an effective add-on therapy to PPIs, acting by reduction of overall reflux burden,(29) but its use is limited by side effects.(4,12,13) New medical therapies overcoming PPI failure with negligible side effects are actively investigated, including potassium-competitive acid blockers.(30) In an era of precision medicine, it is important to evaluate and recommend personalized medical therapies based on individual, rather than group analyses. According to our findings, such a goal can be accomplished by in-depth analysis of on-PPI impedance-pH tracings. Indeed, we detected on-therapy AET higher than the ROC-defined cut-off in nearly half of GERD cases with PPI-refractory heartburn, suggesting that such patients may benefit from incremental acid suppression by potassium-competitive acid blockers. The major strength of our study is represented by the large number of GERD patients who underwent on-PPI impedance-pH monitoring. We admit that the retrospective design could be regarded as a potential bias. However, data collection was carried out prospectively at a referral center where criteria for patient evaluation have long been standardized, and review of impedance-pH tracings was performed by one investigator blinded to clinical details and following rigorous rules for manual analysis.

5 | CONCLUSIONS

We have defined on-PPI cut-offs of conventional and new impedance-pH metrics. Applying such cut-offs, we have shown that comprehensive assessment of impedance-pH tracings, including analysis of PSPW index and MNBI can efficiently characterize PPI-refractory GERD and support treatment escalation.

AUTHOR CONTRIBUTIONS

Marzio Frazzoni, study concept and design; collection, analysis, and interpretation of data; drafting of the manuscript. Leonardo Frazzoni, Mentore Ribolsi, Nicola De Bortoli, Edoardo Savarino: study concept; analysis and interpretation of data; drafting of the manuscript. Salvatore Russo, Rita Conigliaro: study concept; collection, analysis, and interpretation of data; critical revision of the manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors have no conflict of interests related to the present study.

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TABLE 1: Baseline characteristics of 150 GERD cases with PPI-refractory heartburn and 45 GERD cases with PPI-responsive heartburn

	PPI-refractory	PPI-responsive	*p*
Male gender (*n*) (%)	86 (57%)	29 (64%)	0.490
Age (years) (median) (range)	47 (18–79)	55 (19–82)	0.016
Hiatal hernia (*n*) (%)	115 (77%)	23 (51%)	0.025
Erosive reflux disease (*n*) (%)	53 (35%)	6 (13%)	0.005
LES tone (mm Hg) (median) (IQR)	16.8 (11.3–22.2)	18.9 (12.0–23.8)	0.483
ON-PPI SAP >95% and SI >50% for heartburn (*n*) (%)	43 (29%)	-	-
On-PPI gastric acid exposure time (%) (median) (IQR)	41 (26–54)	33 (21–44)	0.062
On-PPI acid refluxes (*n*) (median) (IQR)	12 (5–23)	3 (1–9)	<0.0001
On-PPI weakly acidic refluxes (*n*) (median) (IQR)	36 (17–62)	22 (9–38)	<0.001
On-PPI AET (%) (median) (IQR)	1.0 (0.2–3.2)	0.1 (0.0–0.7)	<0.0001
On-PPI TRs (*n*) (median) (IQR)	56 (36–80)	31 (17–46)	<0.0001
On-PPI PSPW index (%) (median) (IQR)	24 (16–33)	41 (30–50)	<0.00001
On-PPI MNBI (Ω) (median) (IQR)	1813 (1153–2680)	2662 (2053–3048)	0.0001

Note: Erosive reflux disease was defined by erosive esophagitis grade B-C-D Los Angeles score.

Abbreviations: AET, esophageal acid exposure time; IQR, interquartile range; LES, lower esophageal sphincter; MNBI, mean nocturnal baseline impedance; PSPW, post-reflux swallow-induced peristaltic wave; SAP, symptom association probability; SI, symptom index; TRs, total refluxes.

FIGURE 1: ROC curves and AUCs of impedance-pH metrics obtained comparing 150 GERD patients with PPI-refractory heartburn to 45 GERD patients with PPI-responsive heartburn.
AET: acid exposure time; TRs: total refluxes; PSPWI: poast-reflux swallowed induced peristaltic wave index; MNBI: mean nocturnal baseline impedance.

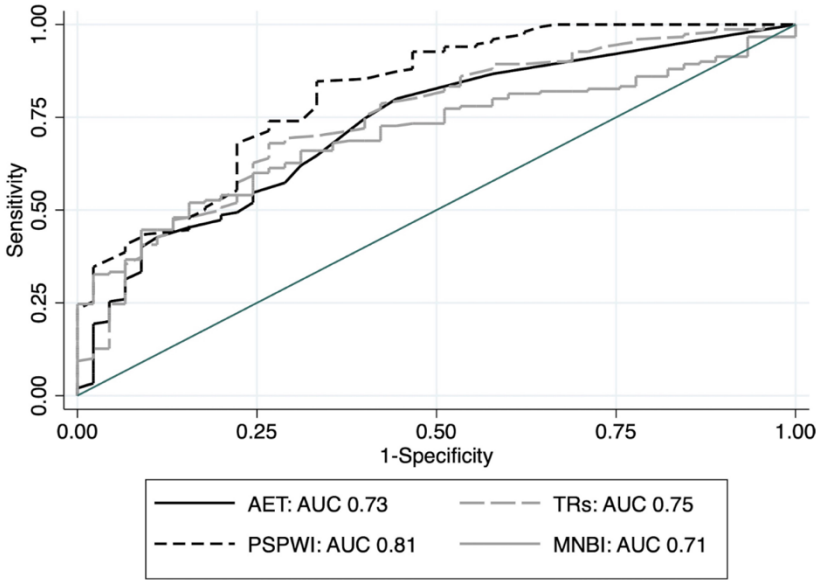

FIGURE 2: AUCs of the ROC-defined on-therapy cut-off of impedance-pH metrics as tested comparing 150 GERD patients with PPI-refractory heartburn to 45 GERD patients PPI-responsive heartburn

AET: acid exposure time; TRs: total refluxes; PSPWI: post-reflux swallowed induced peristaltic wave index; MNBI: mean nocturnal baseline impedance.

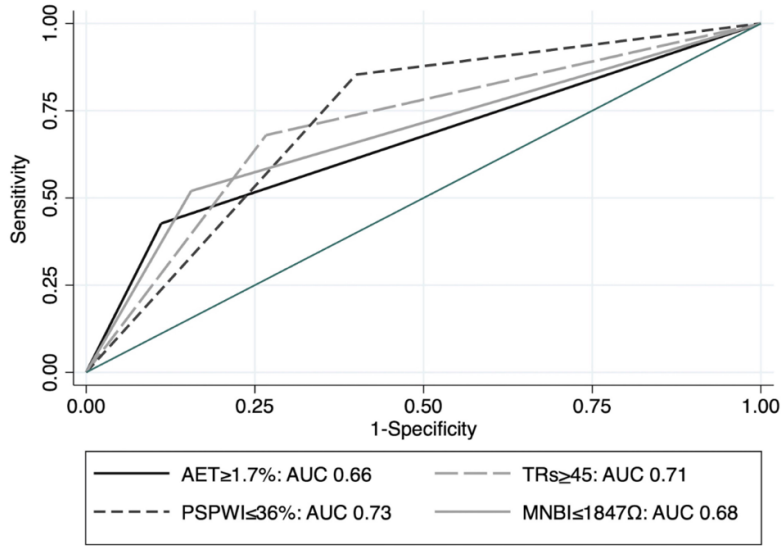

TABLE 2: Positivity of on-therapy impedance pH-impedance metrics according to ROC-defined cut-offs in GERD-patients with PPI-refractory or PPI-responsive heartburn

	PPI-refractory cases (n = 150)	PPI-responsive cases (n = 45)	*P*
AET ≥1.7% (*n*) (%)	64 (43%)	5 (11%)	<0.0001
TRs ≥45 (*n*) (%)	102 (68%)	12 (27%)	<0.0001
PSPW index ≤36% (*n*) (%)	128 (85%)	18 (40%)	<0.0001
MNBI ≤1847 Ω (*n*) (%)	78 (52%)	7 (16%)	<0.0001

Abbreviations: AET, esophageal acid exposure time; MNBI, mean nocturnal baseline impedance; PSPW, post-reflux swallow-induced peristaltic wave; TRs, total refluxes.

TABLE 3: On PPI performance characteristics of the four impedance-pH metrics in characterizing GERD patients with PPI-refractory heartburn

	Sensitivity	Specificity	NPV	PPV
AET ≥1.7%	0.43	0.89	0.32	0.93
TRs ≥45	0.68	0.73	0.41	0.89
PSPW index ≤36%	0.85	0.60	0.55	0.88
MNBI ≤1847 Ω	0.52	0.84	0.35	0.92

Abbreviations

AET: acid exposure time; TRs: total refluxes; PSPWI: post-reflux swallowed induced peristaltic wave index; MNBI: mean nocturnal baseline impedance; NPV: negative predictive value; PPV: positive predictive value.

FIGURE 3: Gain afforded by positivity of PSPW index and/or MNBI added to positivity to AET and/or TRs in 150 GERD patients with PPI-refractory heartburn
AET: acid exposure time; TRs: total refluxes; PSPWI: post-reflux swallowed induced peristaltic wave index; MNBI: mean nocturnal baseline impedance.

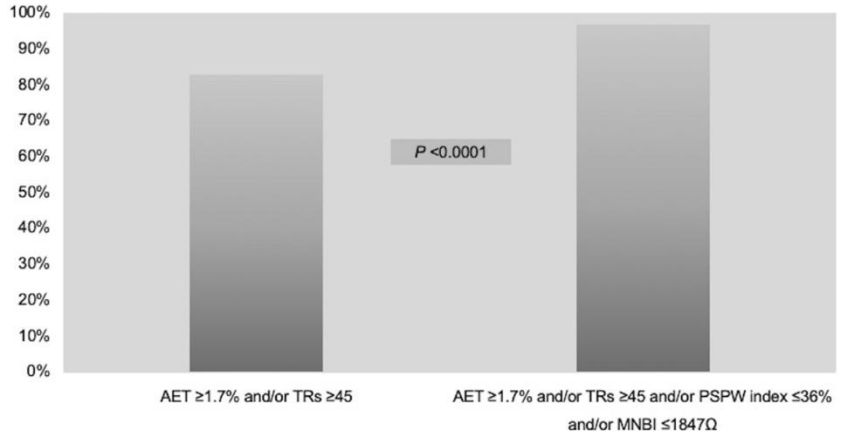

TABLE 4: Comparison of different ROC-defined criteria defining positivity of on-therapy impedance pH-monitoring in PPI-refractory GERD cases.

Criteria	Positivity	*p*
AET ≥1.7% and/or TRs ≥45 and/or PSPW index ≤36% and/or MNBI ≤1847 Ω (*n*) (%)[a]	146/150 (97%)	<0.00001
AET >0.5% and/or TRs >40 (*n*) (%)[b]	114/150 (76%)	

Abbreviations: AET, acid exposure time; TRs, total refluxes; PSPWI, post-reflux swallowed induced peristaltic wave index; MNBI, mean nocturnal baseline impedance.
[a]According to current ROC analysis
[b]According to Gyawali CP, et al. Gastroenterology 2021 (Ref. 16)