THE UNIVERSITY OF MEDICINE AND PHARMACY "CAROL DAVILA" BUCHAREST

DOCTORAL SCHOOL

MEDICINE

Real-time Performance Ranking of Diagnostic Methods for Gastroesophageal Reflux Disease (GERD)

Summary of the Doctoral Dissertation

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1. Introduction

Gastroesophageal reflux disease (GERD) is one of the most common digestive disorders worldwide. According to the 2006 Montreal Consensus, this condition is characterized by the retrograde passage of gastric acid into the esophagus, leading to reflux symptoms (1).

Recent data show that approximately 1.03 billion people suffer from GERD, with a global prevalence of 14% and significant variation depending on geographic location (2). North America has the highest prevalence of GERD at around 19.55%, while Latin America has the lowest prevalence at 12.88% (2). Europe falls between the two continents, with an estimated prevalence of around 14% (2).

Given its high prevalence, GERD is also one of the most expensive digestive diseases due to frequent doctor visits, the cost of treatments and diagnostic tests. In the United States, the costs associated with the diagnosis and treatment of GERD are estimated at $24 billion per year, while in the United Kingdom they reach £760 million.

Thus, considering the costs associated with GERD, correct diagnosis of GERD is paramount. Unfortunately, GERD is an entity that encompasses different phenotypes, and accurate diagnosis of these remains difficult. According to the ROME IV classification, the phenotypes of reflux disease have been defined as: Erosive reflux esophagitis (ERD), Non-erosive gastroesophageal reflux disease (NERD), Functional heartburn (FH) and Reflux hypersensitivity (RH) (3).

In order to facilitate the diagnosis of GERD phenotypes, two new parameters have been recently proposed: mean nocturnal basal impedance (MNBI) and post-reflux swallowing-induced peristaltic wave index (PSPW). MNBI was designed to reflect esophageal mucosal integrity and is defined as the mean basal impedance determined from MII-pH data recorded during three monitoring intervals at night, at 1:00, 2:00, and 3:00 AM for 10 minutes each (4). It can be divided into two types: proximal MNBI, which calculates the mean of the two proximal channels (Z1 and Z2), and distal MNBI, which calculates the mean of the four distal channels (Z3, Z4, Z5, Z6) (5).

PSPW was designed to represent the ability of the esophagus to clear acid after a reflux episode. After an episode of gastroesophageal reflux, the esophageal clearance phenomenon is triggered to protect the esophagus. Esophageal clearance is a biphasic phenomenon, the first component is a secondary peristaltic wave (volume clearance), which rapidly removes some of the refluxed acid from the esophagus, and the second component is a primary peristaltic wave,

triggered by a vagal reflex, which transports salivary bicarbonate and epidermal growth factor to the distal esophageal mucosa, leading to chemical clearance with pH neutralization (6). PSPW is defined as an anterograde impedance decrease of 50% that occurs within the first 30 seconds of the onset of a reflux episode, followed by a return of at least 50% to the initial baseline value.

The scientific objectives of the doctoral thesis were to evaluate the ability of proximal MNBI, distal MNBI, and PSPW to differentiate between GERD phenotypes. The doctoral thesis is divided into two parts: a general part and a special part. The general part presents data from the literature on GERD, including GERD phenotypes and current methods for diagnosing GERD.

In the special part, I conducted a retrospective study on a group of 87 patients diagnosed with gastroesophageal reflux disease, admitted between September 2020 and March 2023 to the Clinical Gastroenterology Department of the Bucharest Emergency University Hospital. The study was conducted in accordance with the Declaration of Helsinki and was approved by the local research ethics committee.

In the doctoral thesis, we showed that distal MNBI and PSPW are good methods for differentiating between the phenotypes of gastroesophageal reflux disease and can be used as complementary methods to esophageal impedance-pH monitoring and upper digestive endoscopy for diagnosis. We also demonstrated that proximal MNBI was an inaccurate method for diagnosing the phenotypes of gastroesophageal reflux disease.

General objectives

The general objectives of the doctoral thesis were as follows:

1. To evaluate the performance of proximal MNBI, distal MNBI, and PSPW in differentiating between ERD patients and non-ERD patients (NERD, RH, and FH)

2. To evaluate the performance of proximal MNBI, distal MNBI, and PSPW in differentiating between patients with abnormal AET (ERD and NERD) and those with normal AET (RH and FH)

3. To evaluate the performance of proximal MNBI, distal MNBI, and PSPW in differentiating between NERD patients and those with normal AET (RH and FH)

4. To evaluate the performance of proximal MNBI, distal MNBI, and PSPW in differentiating between FH patients and the other BRGE phenotypes (ERD, NERD, RH)

5. To evaluate the performance of proximal MNBI, distal MNBI, and PSPW in differentiating between FH patients and RH patients

6. To evaluate the correlation between PSPW and pathological MNBI (MNBI<2292 Ω)

2. Research Methodology

A retrospective study was conducted on a group of 87 patients diagnosed with gastroesophageal reflux disease who were admitted to the Clinical Gastroenterology Department of the Bucharest Emergency University Hospital between September 2020 and March 2023. The study was conducted in accordance with the Declaration of Helsinki and was approved by the local research ethics committee. All patients also signed informed consent prior to inclusion in the study.

The inclusion criteria for the study were:

- Patients aged over 18 years with typical symptoms of gastroesophageal reflux disease (heartburn, acid regurgitation, postprandial epigastric pain) at least twice a week in the last 6 months.

The exclusion criteria for the study were:

- Patients with septal deviation, nasal trauma or nasal obstruction of various etiologies
- Patients with swallowing disorders, such as stroke
- Patients with esophageal obstructions, strictures or fistulas
- Patients with esophageal varices or severe bleeding diathesis
- Patients with a cardiac pacemaker or internal defibrillator
- Pregnant women.
- Patients with excessive alcohol consumption
- Patients with a history of esophageal or gastric surgery

All patients who met the inclusion criteria followed the **study protocol**, which included:

- Clinical examination
- Collection of biological samples (usual)
- Gastroesophageal Reflux Disease Questionnaire (GERDQ)
- Upper digestive endoscopy
- 24-hour esophageal impedance-pH monitoring

Patient classification

Patients were classified into four GERD phenotypes: erosive gastroesophageal reflux disease or erosive reflux esophagitis (ERD), non-erosive gastroesophageal reflux disease (NERD), reflux hypersensitivity (RH), and functional heartburn (FH) based on the Lyon Consensus and Rome IV criteria (3, 7).

ERD was diagnosed in patients with Los Angeles grade C or D esophagitis, peptic strictures, or Barrett's esophagus based on endoscopic examination and abnormal AET (acid exposure time) (>6%). The NERD group was defined by abnormal AET (>6%) with normal endoscopic findings. Patients with normal upper digestive endoscopy findings, normal AET (<4%), and positive SAP (Symptom association probability) were classified as RH. Patients with a negative SAP, normal AET (<4%), and no esophageal mucosal abnormalities on endoscopy were defined as FH.

Mean nocturnal basal impedance (MNBI)

MNBI represents the average basal impedance at three monitoring intervals during the night, at 1:00, 2:00, and 3:00 AM, for a duration of 10 stable minutes in which there are no periods of swallowing, pH drops, and reflux episodes (8). This parameter is measured in ohms (Ω). Proximal MNBI was calculated as the average of the 2 proximal channels (Z1 and Z2), and distal MNBI was calculated as the average of the 4 distal channels (Z3, Z4, Z5, Z6) (5).

Post-swallow reflux-induced peristaltic wave index (PSPW)

PSPW is the primary mechanism of chemical clearance of the esophagus and is defined as a 50% decrease in impedance that occurs within 30 seconds of a reflux event, starting from the most proximal impedance channel and reaching the most distal impedance channel, followed by a return of at least 50% to the initial baseline value. The PSPW index was calculated by dividing the number of PSPW episodes by the number of reflux events (6).

Statistical analysis

IBM SPSS 26 (Statistical Package for the Social Sciences Inc, IBM corporation, Armonk, NY, USA) and Microsoft Office (Microsoft Corporation, One Microsoft Way Redmond, Washington, USA) were used for data analysis. Parameter values were summarized by mean and interquartile range. To compare parameter values between two distinct groups, the non-parametric Mann-Whitney U test was used. When comparing multiple groups, ANOVA analysis was performed. To account for multiple comparisons and maintain the integrity of the statistical analysis, the Bonferroni correction was applied. The correlation between the PSPW index and MNBI was assessed using Pearson's correlation coefficient. Pathological MNBI values were defined in our study as a value below 2292 Ω based on other European studies.

To evaluate the diagnostic performance of parameters such as proximal, distal MNBI, and PSPW, the area under the ROC curve (AUROC) was used. Cut-off values were selected based on the ROC curve with optimal sensitivity and specificity and the best diagnostic performance. A p value less than 0.05 was considered statistically significant.

3. Results

The general characteristics of the study population are presented in Table 3.1. The analyzed study group included 87 patients, of whom 44 were female (50.6%) and 43 were male (49.4%). The etiology of GERD phenotypes was 41.4% with erosive reflux esophagitis (ERD), 21.8% with functional heartburn (FH), 19.5% with reflux hypersensitivity (RH), and 17.2% with non-erosive reflux disease (NERD).

Table 3.1. General characteristics of the study population (n= 87)

Parameter	Values
Age (years)	50.4 ± 11.94
Sex	Men= 43 Female= 44
Etiology	ERD=36 NERD=15 FH=19 RH=17
BMI (kg/m2)	24.59 ± 2.85
DeMeester Score	102 ± 97
AET (percent)	6.48 ± 4.27
MNBI proximal (Ω)	1951 ± 672
MNBI Distal (Ω)	1693 ± 757
PSPW (percent)	41.1 ± 16.64

ERD= erosive reflux disease, NERD= non-erosive reflux disease, FH= functional heartburn, RH= hipersensibility of reflux, BMI=Body Mass Index, AET= Acid Exposure Time, MNBI= Mean Nocturnal Basal Impedance, PSPW= Post-Swallow reflux-induced Peristaltic Wave, Ω=Ohm

In Table 3.2., the characteristics of the study population based on the phenotypes of gastroesophageal reflux disease are presented.

Table 3.2. Characteristics of the study population based on the phenotypes of GERD

	ERD (n=36)	NERD (n=15)	RH (n=17)	FH (n=19)
Age (years)	53 ± 13.5	46.9 ± 8.93	51.4 ± 9	47.2±12.2
Sex	Men = 14 Female = 22	Men =9 Female =6	Men =11 Female =6	Men =9 Female =10
BMI (kg/m2)	24.2 ± 2.2	26.1 ± 4	24.5±2.89	24±2.6
AET (percent)	10.26 ± 2.7	7.9 ± 1.4	2.1 ± 1.24	2.08 ± 1.12
MNBI proximal (Ω)	1689 ± 704	1835 ± 706	2238 ± 576	2284 ± 409
MNBI distal (Ω)	1157 ± 670	1642 ± 696	2129 ± 352	2357±398
PSPW (percent)	29 ± 14.3	41 ± 5.6	48.3±13.6	57.4±10.5

ERD= erosive reflux disease, NERD= non-erosive reflux disease, FH= functional heartburn, RH= hipersensibility of reflux, BMI=Body Mass Index, AET= Acid Exposure Time, MNBI= Mean Nocturnal Basal Impedance, PSPW= Post-Swallow reflux-induced Peristaltic Wave, Ω=Ohm

The performance of proximal MNBI, distal MNBI, and PSPW in differentiating GERD phenotypes is presented in Table 3.3.

Table 3.3. Performance of proximal MNBI, distal MNBI and PSPW in differentiating GERD phenotypes

ERD vs patients non-ERD (NERD, RH, FH)					
	AUROC	Cut-off	Sensitivity	Specificity	*p* value
MNBI proximal	0.683	1521 Ω	80%	50%	0.002
MNBI distal	0.845	1698 Ω	79%	83%	0.001
PSPW	0.849	37.5%	79%	75%	0.001
Patients with abnormal AET (ERD, NERD) vs patients with normal AET (RH, FH)					
	AUROC	Cut-off	Sensitivity	Specificity	*p* value
MNBI proximal	0.708	1818 Ω	83%	57%	0.001
MNBI distal	0.858	1839 Ω	86%	80%	0.001
PSPW	0.856	51%	78%	92%	0.001
NERD vs patients with normal AET (RH, FH)					
	AUROC	Cut-off	Sensitivity	Specificity	*p* value
MNBI proximal	0.646	1918 Ω	78%	60%	0.016
MNBI distal	0.736	1874 Ω	86%	60%	0.001
PSPW	0.794	49%	78%	93%	0.001
RH vs FH					
	AUROC	Cut-off	Sensitivity	Specificity	*p* value
MNBI proximal	0.467	2540 Ω	48%	70%	0.783
MNBI distal	0.695	2164 Ω	73%	53%	0.079
PSPW	0.774	54%	84%	50%	0.03
FH vs others GERD phenotypes (ERD, NERD, RH)					
	AUROC	Cut-off	Sensitivity	Specificity	*p* value
MNBI proximal	0.664	1960 Ω	74%	48%	0.014
MNBI distal	0.833	1925 Ω	84%	70%	0.001
PSPW	0.876	54.5%	84%	82%	0.001

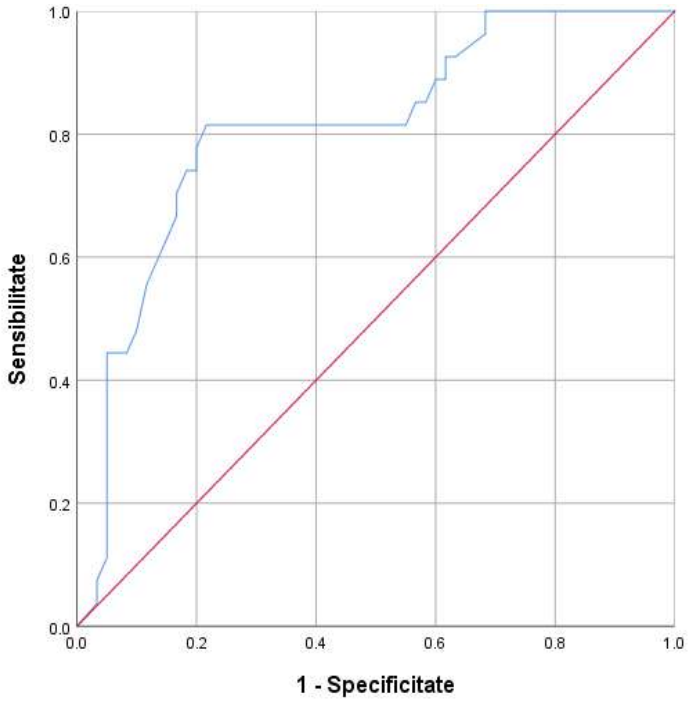
ERD= erosive reflux disease, NERD= non-erosive reflux disease, FH= functional heartburn, RH= hipersensibility of reflux, MNBI= Mean Nocturnal Basal Impedance, PSPW= Post-Swallow reflux-induced Peristaltic Wave

Evaluation of the correlation between PSPW and pathological MNBI (MNBI<2292 Ω)

Since MNBI and PSPW have similar applications and performance in diagnosing BRGE phenotypes, we evaluated whether there is a correlation between the two parameters. First, we used the Pearson correlation coefficient, which was significant (r = 0.725, p = 0.001).

We also investigated whether PSPW could predict pathological MNBI (defined as MNBI < 2292 Ω based on other European studies) (8). PSPW was able to diagnose pathological MNBI with high accuracy with an AUROC of 0.810 (95% confidence interval 0.710-0.910) (Figure 1). For a cut-off value of 47.5%, PSPW was able to predict pathological MNBI with a sensitivity of 81.5% and a specificity of 79%.

Figure 1. ROC curve of PSPW in predicting pathological MNBI (MNBI<2292 Ω)



In Figure 2, we have created a diagnostic algorithm for BRGE phenotypes based on the results of EDS and MII-pH. An alternative algorithm is presented in Figure 3.

Figure 2. Algorithm for diagnosing GERD phenotypes based on Endoscopy and MII-pH

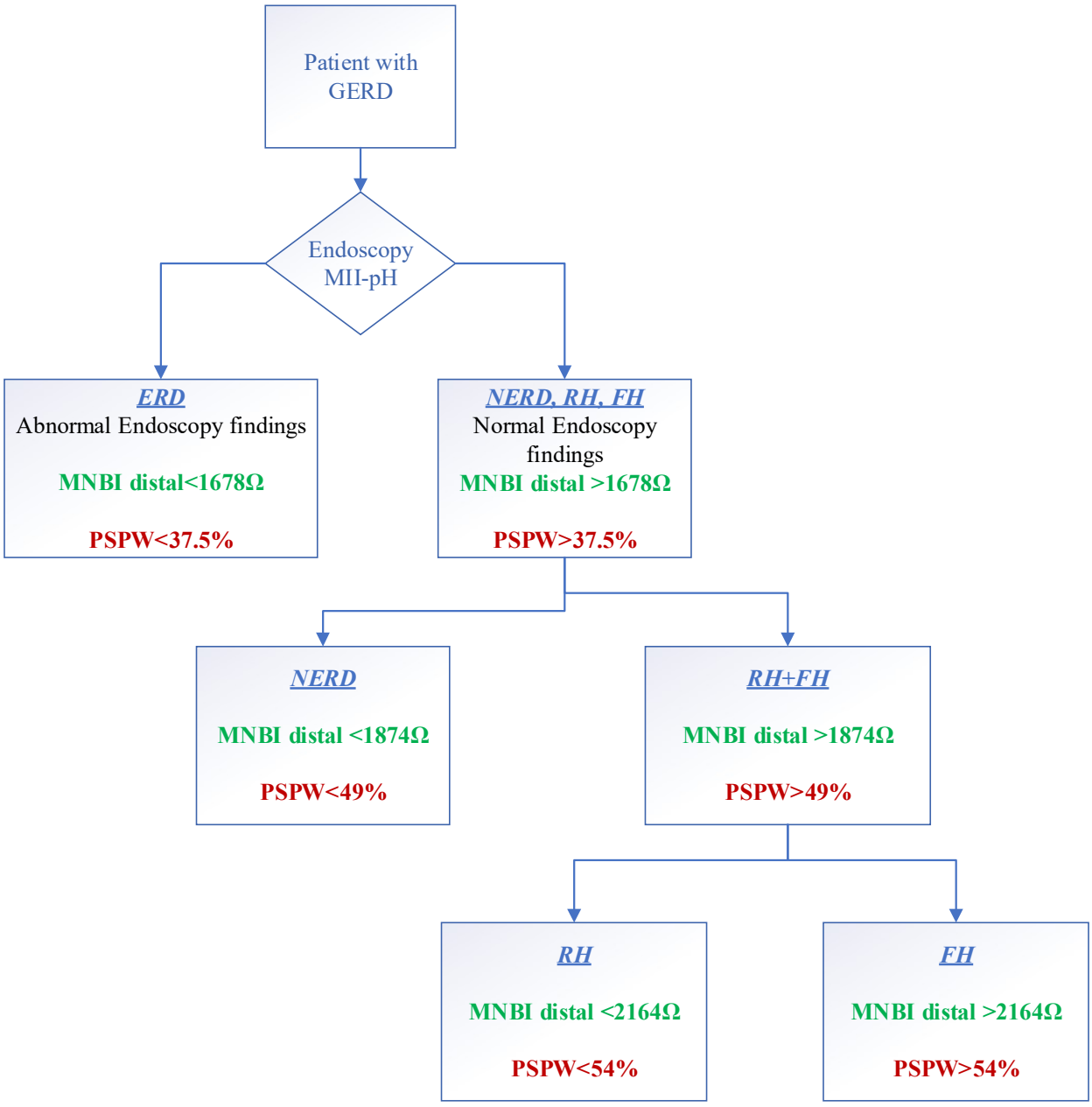
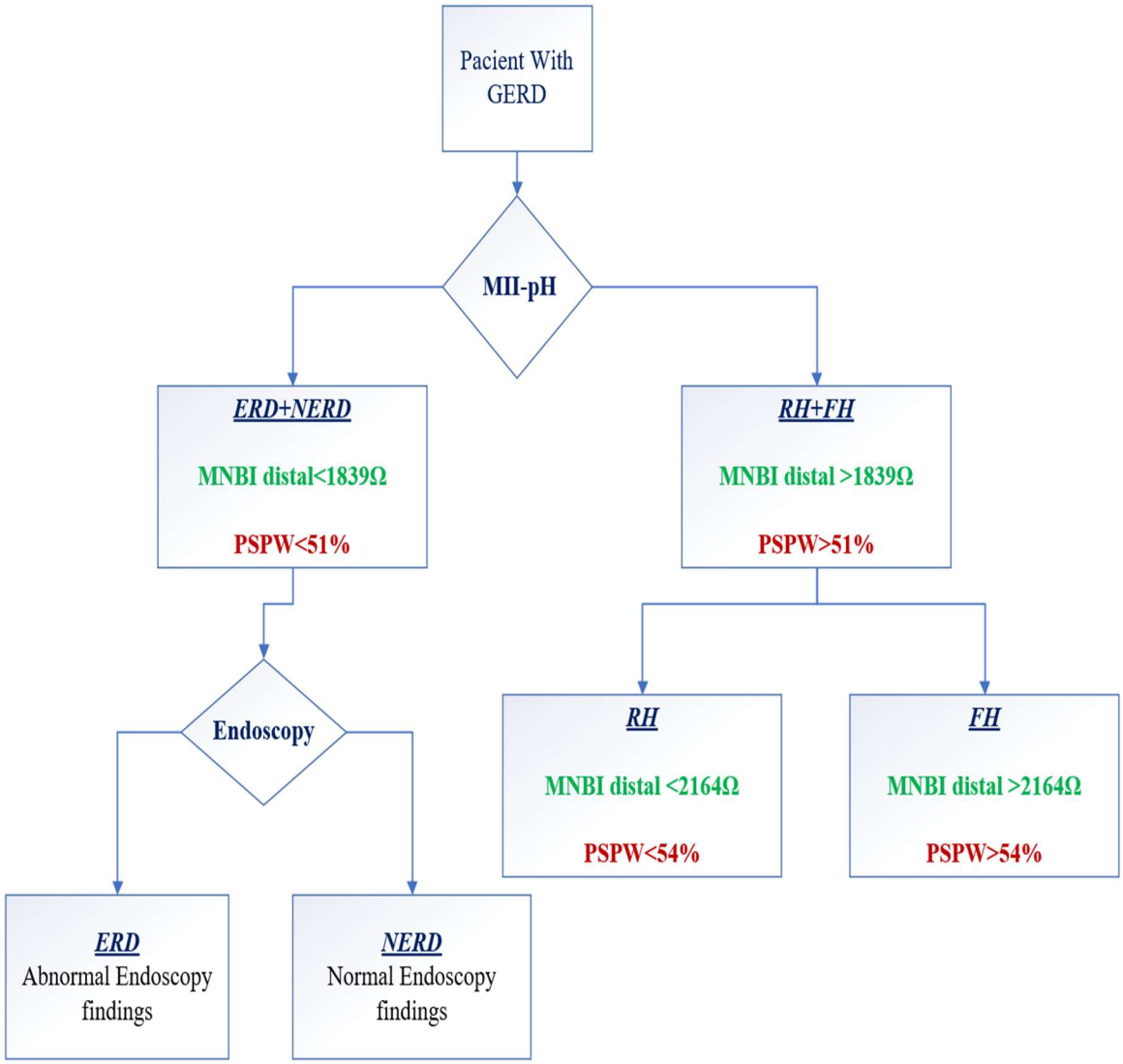


Figure 3. Alternative algorithm for diagnosing GERD phenotypes based on Endoscopy and MII-pH



4. Discussions

For the differentiation of GERD phenotypes, PSPW (AUROC 0.849) and distal MNBI (AUROC 0.845) showed excellent accuracy in separating patients with ERD from those without ERD (NERD, RH, and FH). PSPW (AUROC 0.856) and distal MNBI (AUROC 0.858) also showed very good accuracy in separating patients with abnormal total acid exposure time (AET) (ERD, NERD) from patients with normal total acid exposure time (RH, FH). In addition, PSPW (AUROC 0.794) and distal MNBI (AUROC 0.736) performed well in differentiating patients with NERD from patients with normal AET (RH and FH).

Functional heartburn is considered one of the most common causes of failure of PPI therapy. Therefore, it is essential to correctly diagnose this phenotype, as treatment differs from that of other GERD phenotypes. In our study, PSPW (AUROC 0.876) and distal MNBI (AUROC 0.833) were very good methods for distinguishing patients with FH from the other phenotypes of gastroesophageal reflux disease. PSPW (AUROC 0.774) also showed good accuracy in separating patients with FH from those with RH.

Given that MNBI and PSPW have similar applications, our study found that PSPW values were associated with the presence of pathological MNBI (<2292 Ω). For a cutoff value of 47.5%, PSPW was able to predict the presence of pathological MNBI with a sensitivity of 81.5% and a specificity of 79%.

Our study had several limitations. First, it was a retrospective analysis conducted at a single medical center, which could have introduced selection bias. Second, we had a small sample size of patients, did not include healthy patients or patients taking proton pump inhibitors. Finally, we calculated MNBI and PSPW manually, as no software application was available at the time for automatic calculation.

The strength of our study lies in the simultaneous measurement of MNBI and PSPW in multiple GERD phenotypes, while revealing a significant correlation between these two parameters. Further studies need to be elaborated to confirm the viability of MNBI and PSPW for the diagnosis of GERD phenotypes, as well as the need to establish standard cut-offs depending on the MII-pH device used and the geographical region.

5. Conclusions

- Distal mean nocturnal baseline impedance (MNBI distal) and the post-reflux deglutition-induced peristaltic wave index (PSPW) are good methods for differentiating gastroesophageal reflux disease phenotypes and can be used complementary to esophageal impedance-pH monitoring and upper gastrointestinal endoscopy for diagnosis.
- Proximal mean nocturnal baseline impedance (MNBI proximal) was an inaccurate method for diagnosing gastroesophageal reflux disease phenotypes.
- The post-reflux deglutition-induced peristaltic wave index (PSPW) (AUROC 0.849) and distal mean nocturnal baseline impedance (MNBI distal) (AUROC 0.845) showed very good accuracy in differentiating patients with erosive reflux esophagitis (ERD) from patients without erosive reflux esophagitis (ERD) and those with non-erosive reflux disease (NERD), reflux hypersensitivity (RH) and functional heartburn (FH).
- The post-reflux deglutition-induced peristaltic wave index (PSPW) (AUROC 0.856) and distal mean nocturnal baseline impedance (MNBI distal) (AUROC 0.858) showed very good accuracy in separating patients with abnormal total acid exposure time (AET) (ERD, NERD) from patients with normal total acid exposure time (AET) (RH, FH).
- The post-reflux deglutition-induced peristaltic wave index (PSPW) (AUROC 0.794) and distal mean nocturnal baseline impedance (MNBI distal) (AUROC 0.736) performed well in differentiating patients with non-erosive reflux disease (NERD) from patients with normal total acid exposure time (AET) (reflux hypersensitivity (RH) and functional heartburn (FH)).
- The post-reflux deglutition-induced peristaltic wave index (PSPW) (AUROC 0.876) and distal mean nocturnal baseline impedance (MNBI distal) (AUROC 0.833) were very good methods for distinguishing patients with functional heartburn (FH) from the other phenotypes of gastroesophageal reflux disease (erosive reflux esophagitis, non-erosive reflux disease, reflux hypersensitivity).
- To differentiate patients with reflux hypersensitivity (RH) from those with functional heartburn (FH), the post-reflux deglutition-induced peristaltic wave index (PSPW) (AUROC 0.774) was superior to distal mean nocturnal baseline impedance (MNBI distal) (AUROC 0.695).

- There is a significant correlation between pathological mean nocturnal baseline impedance - pathological MNBI (MNBI<2292 Ω) and the post-reflux deglutition-induced peristaltic wave index (PSPW). The post-reflux deglutition-induced peristaltic wave index (PSPW) was able to predict the presence of pathological MNBI (MNBI<2292 Ω) with good performance (AUROC of 0.810).
- Further studies need to be conducted to confirm the viability of distal MNBI and PSPW for the diagnosis of gastroesophageal reflux disease (GERD) phenotypes, and it is also necessary to establish standard cut-offs depending on the esophageal impedance-pH monitoring (MII-pH) device used and the geographical region.
- The post-reflux deglutition-induced peristaltic wave index (PSPW) and distal mean nocturnal baseline impedance (MNBI distal) can be used to facilitate the diagnosis of GERD phenotypes when standard parameters provide inconclusive results.

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Original Articles

1. **Sararu ER**, Peagu R, Fierbinteanu-Braticevici C. Association between Mean Nocturnal Baseline Impedance (MNBI) and Post-Reflux Swallow-Induced Peristaltic Wave Index (PSPW) in GERD Patients. Diagnostics (Basel). 2023 Dec 5;13(24):3602. doi: 10.3390/diagnostics13243602. PMID: 38132186; PMCID: PMC10742549.
https://www.mdpi.com/2075-4418/13/24/3602
Impact factor 3.6

2. **Sararu R**, Peagu R, Fierbinteanu-Braticevici C. The Role of Distal Mean Nocturnal Baseline Impedance in Differentiating GERD Phenotypes. J Gastrointestin Liver Dis. 2023 Sep 28;32(3):291-297. doi: 10.15403/jgld-4669. PMID: 37774210
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Impact factor 2.1

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3. **Săraru ER**, Enciu V, Peagu R, Fierbinţeanu-Braticevici C. Advances in the diagnosis of GERD. Rom J Intern Med. 2021 Mar 5;59(1):3-9. doi: 10.2478/rjim-2020-0027. PMID: 33010143.
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