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Clinical Features and Diagnostic Reliability in Paediatric Laryngopharyngeal Reflux

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Abstract

Objective: The aim of this study was to assess the validity of current diagnostic approaches in pediatric laryngopharyngeal reflux (PLPR). Clinical status findings and 24h double probe oesophageal pH monitoring results in children with suspected PLPR and/or GERD were analyzed and a clinically useful probability score was developed.

Methods: This is a retrospective longitudinal cohort study including 89 pediatric patients who underwent preliminary oropharyngoscopy, and then nasal fibre optic laryngoscopy and ambulatory 24h oesophageal pH monitoring in a tertiary pediatric and otorhinolaryngology hospital center. The patients' parents gave written informed consent for diagnostic testing. Statistical analysis was performed using standard descriptive statistics. Associations between variables were assessed using Fisher's exact test, Mann-Whitney test and Kruskal-Wallis test for non-parametric paired samples.

Results: Patients' age spanned 1 to 18 years with a median of 11.2. Out of the 89 patients, 56 were girls, and 33 were boys. All of the patients underwent nasal fibre optic laryngoscopy and 24h double probe pH monitoring. Out of 89 examined children, 50 had PLPR. Out of the 50 positive for PLPR, 46 had a positive clinical finding, with a sensitivity of 92% (95% CI: 80.75%-97.73%) and specificity of 10.26% (95% CI: 2.93%-24.24%). Boys have GERD significantly more often than girls ($p<0.0001$), and have a worse result of pH monitoring ($p<0.0001$). The most common finding was an injected and granulated oropharynx accompanied by posterior laryngitis (54/89). Patients with leading symptoms of asthma had significantly worse GERD scores ($p=0.0493$). The patients were then reassigned to newly developed risk categories and significant correlation with a positive PLPR diagnosis was found ($p=0.0262$).

Conclusions: The significance of a thorough otorhinolaryngologic and paediatric examination and patient history taking is still paramount, with additional benefit in diagnosing the disease arising from 24h oesophageal pH monitoring in select patients. This study brings to light new relationships between clinical symptoms and objective findings and presents a novel attempt to classify the diagnosis likelihood. Patient stratification could help clinicians in defining groups at high risk and support a timely, cost-effective and precise diagnostic evaluation and proper therapy.

Keywords: diagnosis; pediatric laryngopharyngeal reflux; clinical finding; pH monitoring

Background

Pediatric laryngopharyngeal reflux (PLPR) is a common pediatric disorder that remains insufficiently illuminated. The importance of this disease is enhanced when considering that it is frequently linked with comorbidities and overlooked by otorhinolaryngologists and paediatricians. Laryngopharyngeal reflux (LPR) refers to the backflow of stomach contents into the throat, that is, into the laryngopharynx. The symptom complex is associated with acid-induced and pepsin-mediated injury to the mucosa of the larynx and pharynx. There is evidence that LPR is associated with rhinosinusitis, laryngitis, pneumonia, and asthma in children [1]. Another issue is overlapping with similar diagnoses such as GERD and GER which makes a reliable diagnosis uncertain in everyday practice among pediatric otorhinolaryngologists and paediatricians. Gastroesophageal reflux disease refers to gastrooesophageal reflux that is excessive and that causes tissue damage and/or clinical symptoms. Children with PLPR often do not experience classic GERD symptoms and symptoms may occur intermittently, which makes the diagnosis even more challenging [2]. Currently published studies shed little light on correlation of respiratory symptoms,

endoscopic findings and results of frequently used diagnostic tests [3]. One of the most commonly-used techniques to document LPR is ambulatory 24h pH monitoring. When paired with nasal fibre optic laryngoscopy, it represents a minimally invasive and least time-consuming method for detecting PLPR [3, 4].

Objective

The aim of this study was to assess the validity of current diagnostic approaches in PLPR. We examined clinical status findings and 24h double probe oesophageal pH monitoring results in children with suspected PLPR and/or GERD and developed a clinically useful probability score combining clinical findings and 24h pH monitoring results.

Methods

This is a retrospective longitudinal cohort study including 89 pediatric patients who underwent oropharyngoscopy, fibre optic larygoscopy and 24h oesophageal pH monitoring due to suspect symptoms in their medical history suggesting PLPR; chronic coughing, hoarseness of voice, chronic laryngitis, postnasal discharge and frequent throat clearing and asthma. There were three patients with a combination of asthma and allergic rhinitis that were included in the study, but the patients were evaluated out of their respective allergen season to avoid misinterpretation of the clinical findings and all three were symptom free regarding the nasal and ocular manifestations of allergic rhinitis. A correlation between local findings of PLPR and (hetero) anamnestic data as subjective factors, and objective data obtained by 24-hour dual-probe monitoring were analyzed. The study was carried out in a period from January 1st, 2007 and December 31st, 2012 in a tertiary pediatric and otorhinolaryngology hospital center (Clinical Hospital Centre Sestre milosrdnice, Zagreb, Croatia). This study and its protocol were approved by the University Hospital Centre Sestre milosrdnice Bioethical

Board adhering to the Helsinki Declaration of 1983, and informed consent was obtained from all of the patients' parents and legal guardians. After overnight fasting, a 24h double-probe pH monitoring was performed (Flexilog 2000, Dual Channel Recorder, Oakfield Instruments Ltd, Witney, UK**)** using a trans-nasally placed catheter (ComfortTecPlus, Sandhill Scientific, Highland Ranch, Co,USA), and pH recorder (Flexisoft III, Oakfield Instruments Ltd, Witney, UK). Standard protocol 24h pH monitoring was conducted [5]. Following calibration at 37 °C in pH 7.01 and pH 1.07 buffer solution (Standard instruments GmbH, Karlsruhe, Germany) before each study, the double-sensor arm was introduced trans-nasally and advanced until gastric pH was reached by the distal sensor. The probe was then withdrawn slowly until the distal sensor showed an abrupt increase in pH value, and then the probe was withdrawn another 5cm and fixed to the nose, adjusting to the age and heights of patients. When probe misalignment due to inadequate test results was suspected, a chest X-ray was performed and the probe was realigned. All of the patients were fed with their normal formulas or usual diet during pH monitoring. Oesophageal pH was recorded in supine, upright, and postprandial positions. A positive test criterion for diagnosis of GERD was considered as ≥5% of total time with pH<4. At least three episodes of pH below 4 in the proximal probe with a simultaneous drop or a preceding decrease of pH<4 in the distal probe or ≥1% for the percentage of total time pH<4 in the proximal probe were accepted as PLPR. The reflux, Boix-Ochoa and DeMeester-Johnson indexes, number of acid reflux events lasting >5 min and duration of the longest reflux were also noted. Ambulatory 24h double-probe pH monitoring was applied by the same paediatric gastroenterologist. The otorhinolaryngologic examination was performed by the same otorhinolaryngologist, including nasal fibre optic laryngoscopy (4mm flexible optic fibre, Storz Videolaryngoscope 11001R01 Karl Storz, Tuttlingen, Germany) that assessed the upper airway from the nasal vestibule to the infraglottic area and the oral cavity/oropharynx. The patients' parents gave written informed consent for diagnostic testing.

Statistical analysis was performed using MedCalc software (Version 11.2.1 © 1993-2010. MedCalc Software bvba Software, Broekstraat 52, 9030 Mariakerke, Belgium), using standard descriptive statistics and frequency tabulation as indicated. The data for the n=89 cohort were expressed as ratios due to n<100. Associations between variables were assessed using Fisher's exact test, Mann-Whitney test and Kruskal-Wallis test for non-parametric paired samples. All tests of statistical significance were performed using a two-sided 5% type I error rate.

Results

The study included 89 pediatric patients aged 1 to 18 years (median age was 11.2). All of them underwent fibre optic laryngoscopy. Out of the 89 patients, 56 were girls, and 33 were boys. All of the patients underwent 24h double probe pH monitoring. Out of 89 examined children, 50 had PLPR. Out of the 50 positive for PLPR, 46 had a positive clinical finding after medical history taking, oropharyngoscopy and nasal fibre optic laryngoscopy, with a sensitivity of 92% (95% CI: 80.75%-97.73%) and specificity of 10.26% (95% CI: 2.93%-24.24%). Positive predictive value was 56.79%, and negative predictive value was 50% (Figures 1 and 2). Further data analysis showed that boys tend to have GERD significantly more often than girls (Mann-Whitney U test, $p<0.0001$), and have a worse result of pH monitoring (Mann-Whitney U test, $p<0.0001$). The reflux index numeric value obtained through pH monitoring was significantly higher in patients with more advanced forms of the disease, with a cut-off value of 5%, median value of 3,5% (0,2-68.7%) (Kruskal-Wallis test, $p<0.001$, Figure 3). The most common finding was an injected and granulated oropharynx accompanied by posterior laryngitis (54/89), followed by an injected and granulated oropharynx (14/89), posterior laryngitis (10/89), normal finding (10/89), and vocal nodules

(1/89). The patients were then divided into 5 diagnostic groups according to their leading symptoms: prolonged coughing (28/89), asthma + coughing (15/89), asthma (33/89), dysphonia + coughing (7/89) and chest pain (6/89). Out of all 5 symptom groups, dysphonia + coughing was least likely to be statistically correlated to a positive PLPR diagnosis and more advanced GERD grades (Kruskal-Wallis test, p=0.0133, Figure 4). Patients groups with leading symptoms of asthma and asthma + coughing were statistically significantly correlated with a positive PLPR diagnosis and higher GERD grades (Kruskal-Wallis test, p=0.0493, Figure 5). When gastrointestinal comorbidity was analyzed, 47/89 children had no apparent symptoms, 15/89 complained of epigastric pain, 14/89 had occasional nausea, 10/89 experienced regurgitation, and 3/89 complained of tasting acid in their oral cavity. After the patients had been assigned to newly developed risk categories, a significant correlation with a positive PLPR diagnosis was found (Kruskal-Wallis test, p=0.0262, n=89). Proton pomp inhibitors (PPIs) were given to all of the patients diagnosed with moderate and severe PLPR by 24h double-probe pH monitoring.

Discussion

A reliable diagnosis of PLPR can, at times, be elusive. The typical pattern of symptoms is chronic-intermittent and the diagnosis is anything but straight-forward [6]. Controversial issues are numerous, encompassing clinical manifestations, diagnostic testing, interpretation of findings and treatment. Determining the relationship between PLPR and local laryngeal and pharyngeal findings can be a complex task, even more so considering limited reliability of diagnosis based on local findings [7, 8, 9, 10, 11]. Even when the diagnosis of PLPR is based on 24-hour dual-probe pH monitoring results, it may still be inaccurate since its sensitivity is low and the incidence of false-negative results is as high as 25–50% [10]. The limitations of

diagnosing the disease based on isolated patient symptoms accompanied solely by pH testing have prompted investigators to quantify laryngeal findings attributed to reflux [11]. The distinction between GERD and PLPR is based on their pathophysiology, symptoms and sequelae, with a majority of PLPR presenting with atypical GERD symptoms [12]. Most frequently, respiratory symptoms are present, but difficult to assess objectively. A wide variety of otorhinolaryngologic symptoms may be seen and a correlation with asthma comorbidity has been noted [13]. Even with an absence of specific clinical presentations, hoarseness, dysphonia, postnasal drip with repetitive throat clearing, chronic cough, laryngeal spasm and dysphagia are common symptoms of PLPR [14, 15, 16]. In our study, 50 out of 89 children were diagnosed with PLPR by 24h oesophageal probe pH monitoring. Oesophageal probe pH monitoring was performed in all children due to the fact that they were referred to our clinic by pediatric gastroenterologists who had previously suspected a possible GERD/LPR diagnosis. This protocol specificity reflects the practice environment of a tertiary clinical centre and a close collaboration between pediatricians and otorhinolaryngologists. In most cases, the pediatricians are the first to suspect and test for possible GERD, and rely on otorhinolaryngologists to examine the child for possible extraoesophageal manifestations of the disease when respiratory simptoms were present. Since a large proportion of children had mild GERD or no GERD at all after pH monitoring, the LPR diagnosis was made on a representative sample of children that was not biased by previously negative nasal fibre optic laryngoscopic findings. Out of the 50 patients with a positive diagnosis, 46 had a positive clinical finding (92% sensitivity), with a significantly higher incidence in boys, although they accounted for only a third of our study subjects (33/89). Boys also tended to have more advanced GERD levels, according to 24h oesophageal pH monitoring results. All of our patients had signs of respiratory distress at initial evaluation, and the most frequent was an injected and granulated oropharynx accompanied by posterior laryngitis (54/89). When

considering all of the recorded signs, oropharynx injection and granulation was noted in 69/89 patients, with an additional 10 showing isolated signs of posterior laryngitis. Gastrointestinal comorbidity was recorded in 42 out of 89 patients, with epigastric pain (15/89) being the most common finding, followed by nausea (14/89), regurgitation (10/89), and acid aftertaste in the oral cavity (3/89). When examining their medical histories, 48/89 patients with combined asthma or combined asthma and chronic coughing showed a higher incidence of GERD levels. Combined dysphonia and coughing was least likely to be statistically correlated to a positive PLPR diagnosis. There have been few studies to date on correlation of clinical presentation in PLPR and diagnostic accuracy by objective testing [8, 17, 18, 19, 20, 21, 22]. Published studies report varying positive fibreoptic larygoscopic rates, ranging from only 40% to 90%, whereas we report a significantly higher sensitivity rate (92%), but a low specificity rate (10%), which is likely attributed to differing subjective fibre optic examination criteria [8]. Other studies included bronchoscopy findings into their analyses and report laryngeal abnormalities in up to 83% of all children that underwent fibre optic examinations and had a positive PLPR diagnosis [21]. Published studies list postglottic and/or arytenoid oedema and vocal fold oedema as leading signs in the majority of patients, which is only partially the case in our study [19, 20]. We found that the combination of oropharyngeal erythema and posterior commissure erythema is the most frequent finding and correlates well with pH monitoring and PLPR diagnosis confirmation. Most published studies favor the use of fibre optic larygoscopy as a method of clinical assessment that shows high predictive value, but there are very few attempts to organize the abundance of possible findings into a diagnostic probability score, especially in the paediatric population [19, 20, 21, 22]. Studies with the highest sensitivity included various indications for endoscopy, such as tracheostomy surveillance, noisy breathing, dysphonia, chronic cough, laryngotracheal reconstruction follow-up, oxygen desaturation, tracheal or subglottic stenosis, bronchial biopsy, and

recurrent pneumonia, whereas our study included patients with suspected PLPR, but still retained adequate sensitivity. This can be further improved through using a simple tool for improving diagnostic probability. According to data gathered in our study, a probability of diagnosis score was constructed in order to help clinicians with reaching an early and correct diagnosis, which then leads to proper and cost-effective treatment [8, 13].

The most reliable clinical symptoms that can lead to the diagnosis of LPR in children are the following: chronic coughing, chronic throat clearing, dysphonia, halitosis, nausea, epigastric pain. The most frequent accompanying local findings include: redness and granulation of the posterior oropharyngeal wall, posterior commissure and/or arythenoid erythema and edema and vocal nodules. When comorbidity is concerned, asthma, recurrent laryngitis and obesity are most frequent with PLPR [23].

Every group (clinical symptoms alongside local findings, comorbidity and obesity) is marked by one point and depending on the score (0-3), a clinical diagnosis of PLPR can be considered. If at least one positive symptom from the symptom group is present, a point is added (Table 1), so that the patients are divided into 3 risk groups, based on clinical criteria: 1. patients that have a high probability score for PLPR (3 points), 2. patients that have a moderate probability score for PLPR (2 points), 3. patients that have a low probability for PLPR score (0-1 point).

When we retrospectively assign points to the appropriate patient groups (Table 1), 49 had a low risk for PLPR, 25 had a moderate risk, and 15 had a high risk for PLPR. After additional data analysis, the patient groups show a significant correlation with a positive PLPR diagnosis through “gold standard” pH monitoring results (Figure 6, Kruskal-Wallis test, p=0.0262, n=89). Additional correlation is shown with respective GERD grades that confirm that the scoring system functions well not only for PLPR, but also for GERD stratification (Figure 7,

Kruskal-Wallis test, p=0.0020, n=89). Since the presence of clinical findings of PLPR has very high sensitivity but very low specificity, and both the positive and negative predictive values are close to 50%, developing a heuristic model for certain constellations of symptoms/findings was necessary. When analyzing the correlation between certain symptom and finding groups, it became apparent that some combinations are statistically positively correlated to a positive PLPR diagnosis. Various combinations of symptoms, local findings and comorbidities were analyzed. Patients that had a combination of asthma and posterior laryngitis alongside oropharyngeal wall redness were significantly more often connected to moderate and high risk PLPR groups. Patients with prolonged coughing combined with no posterior laryngitis or patients with isolated hoarseness regardless of their clinical finding were significantly less often placed in moderate and high risk PLPR groups (Figure 8, Kruskal-Wallis test, p=0.0086, n=89). Developing a probability score based on additive features enables a logical and helpful assessment of PLPR risk and could prove useful in an everyday clinical setting. The level of diagnostic reliability correlated well with PLPR objective diagnostics, which supports the need for risk stratification. Further investigation on a larger patient population is needed to improve on the stratification's specificity, especially considering that empirical IPP treatment is often prescribed to suspected PLPR patients without risk group stratification and based on loosely interpreted evidence-based data that supports empirical IPP therapy in the paediatric population [24]. Our standard practice includes recommending diet alterations to all low risk and some moderate risk patients, after which regular check-ups should be performed. If the treatment protocol proves insufficient in controlling the symptoms, further testing in a tertiary institution coupled with 24h oesophageal pH monitoring should be performed. All high risk patients should be examined in a tertiary center, with 24h pH monitoring and fibre optic laryngoscopy performed and appropriate IPP treatment administered accordingly [24].

Conclusion

Paediatric laryngopharyngeal reflux is an important entity to consider when dealing with patients with unexplained respiratory symptoms. The significance of a thorough otorhinolaryngologic and paediatric examination and patient history taking is still paramount, with additional benefit in diagnosing the disease arising from 24h oesophageal pH monitoring in select patients. This study brings to light new relationships between clinical symptoms and objective findings and presents a novel attempt to classify the diagnosis likelihood. Patient stratification could help clinicians in defining groups at high risk and support a timely, cost-effective and precise diagnostic evaluation and proper treatment.

Conflict of interest statement

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript.

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Figures and captions

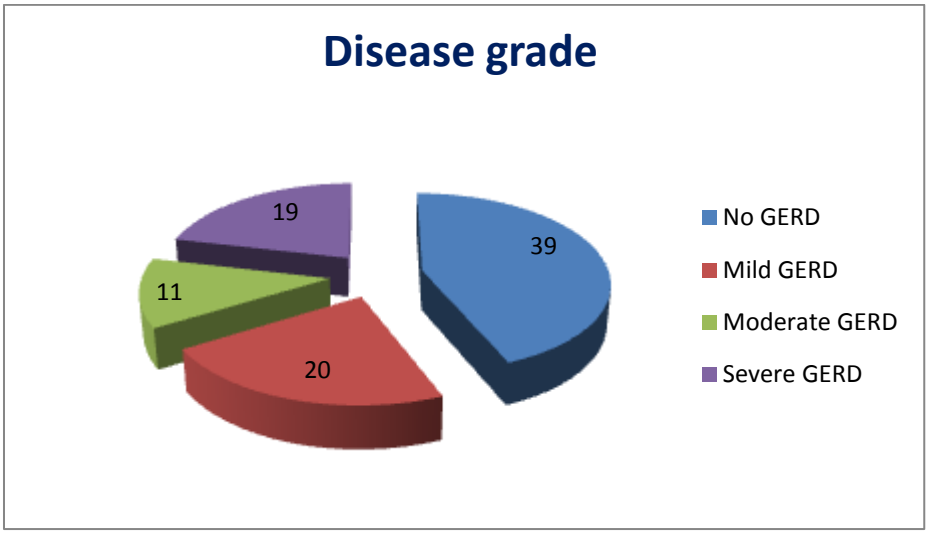

Figure 1. Distribution of GERD according to severity (n=89).

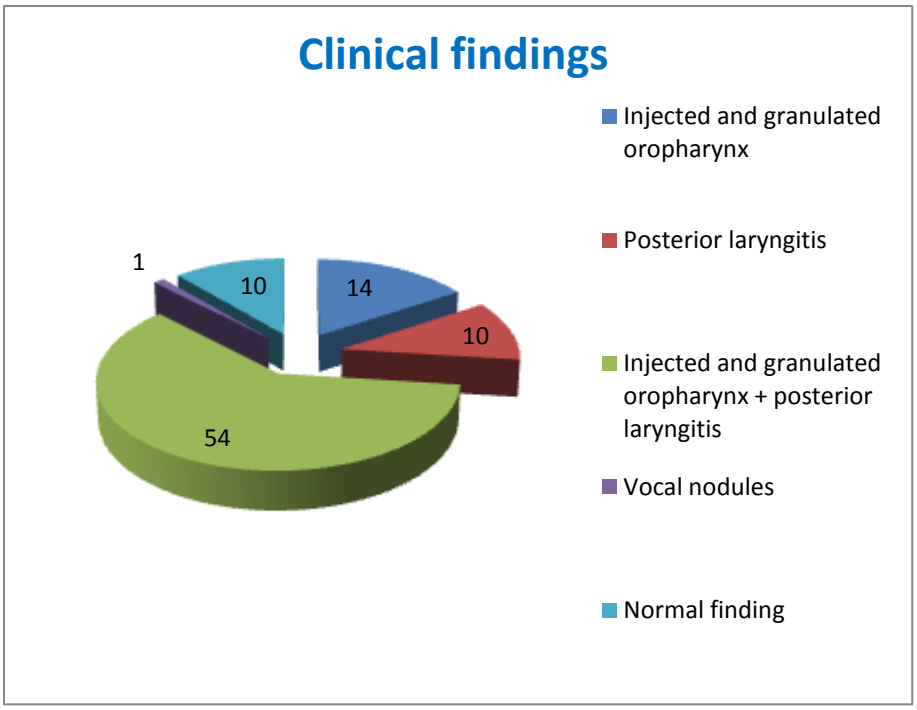

Figure 2. Distribution of clinical findings (n=89).

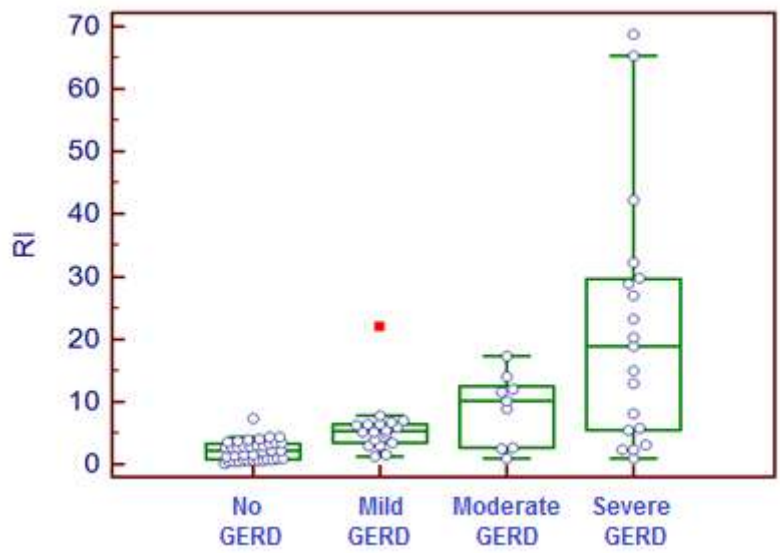

Figure 3. Correlation between rising reflux score and GERD disease grade (Kruskal-Wallis test, $p<0.0001$, n=89).

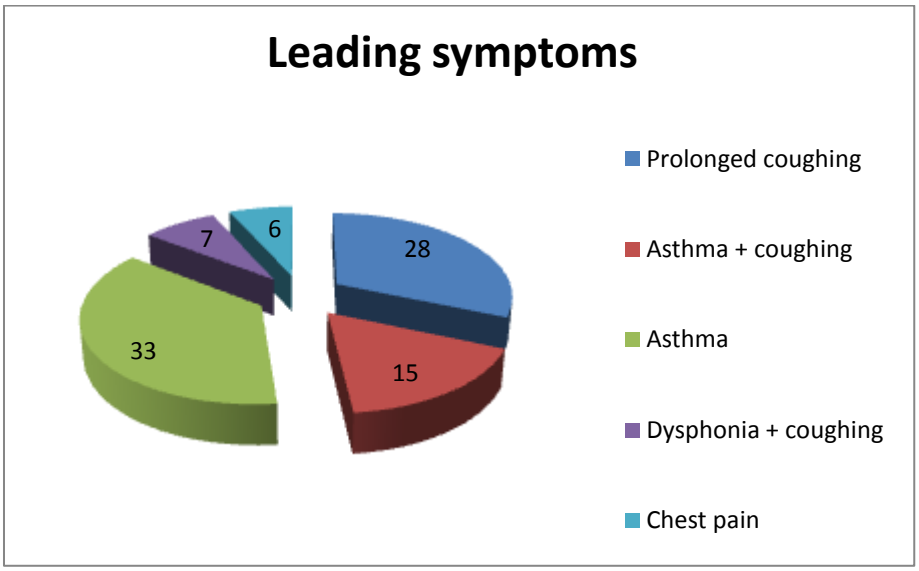

Figure 4. Distribution of leading symptoms at presentation (n=89).

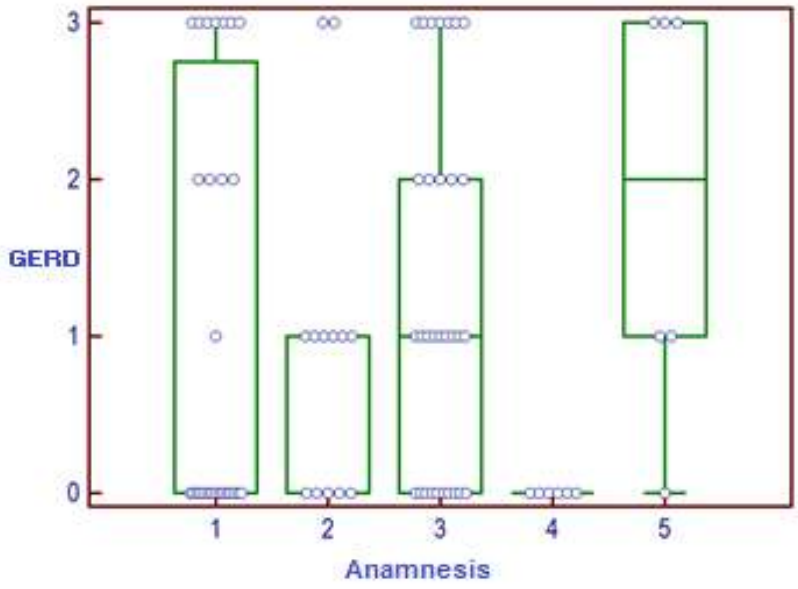

Figure 5. Correlation between disease grade and leading symptoms: 1 - prolonged coughing, 2 - asthma + coughing, 3 - asthma, 4 - dysphonia + coughing, 5 – chest pain (Kruskal-Wallis test, p=0.0493, n=89).

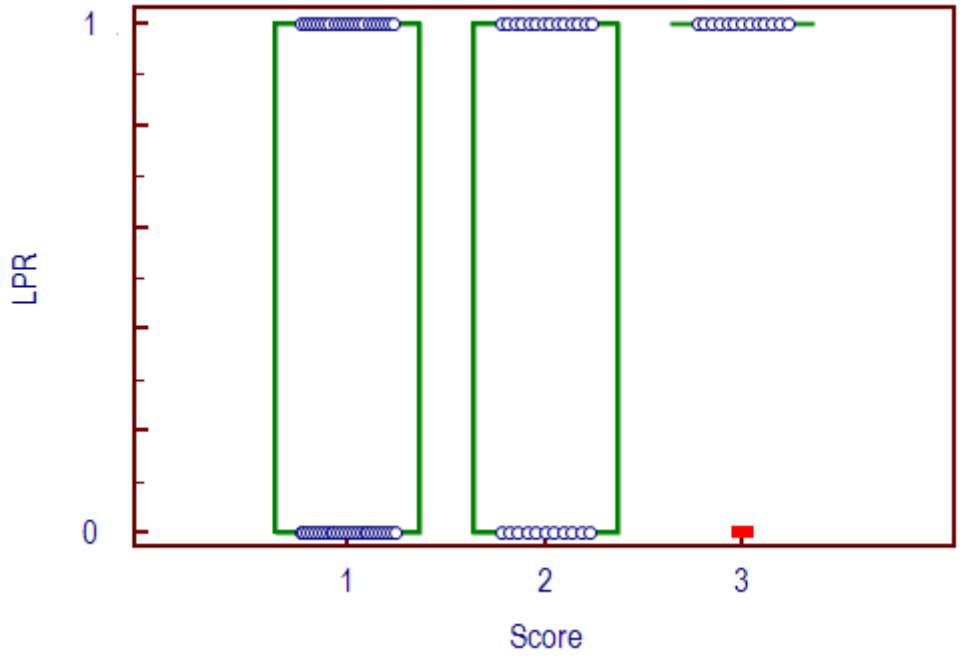

Figure 6. Correlation between PLPR diagnosis through 24h pH monitoring and probability scoring using a new probability tool proposed by the authors (Kruskal-Wallis test, *p*=0.0262, n=89).

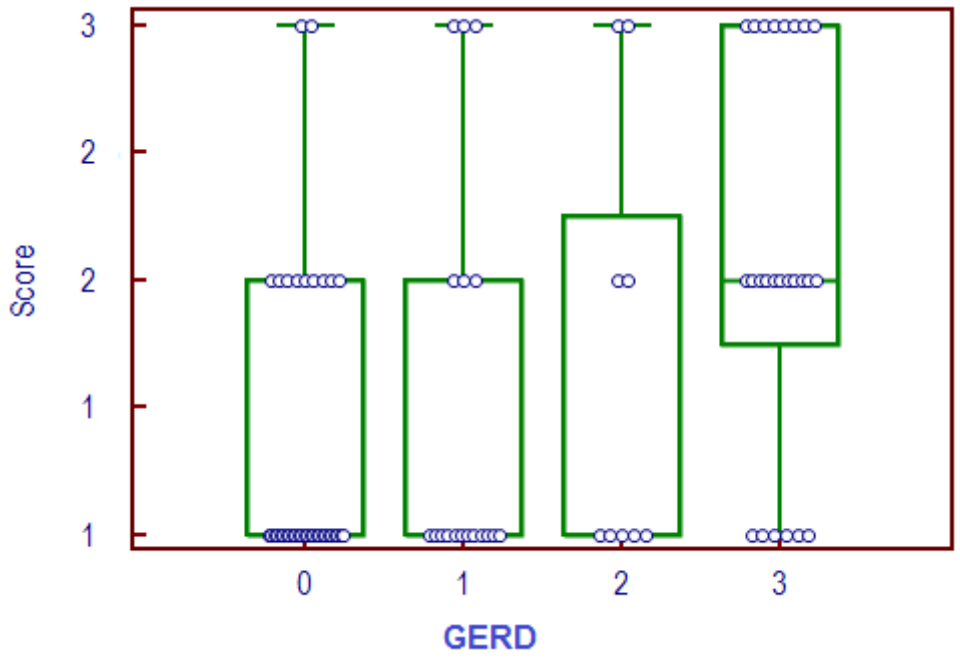

Figure 7. Correlation between rising GERD grades and the newly proposed probability scoring tool (Kruskal-Wallis test, *p*=0.0020, n=89).

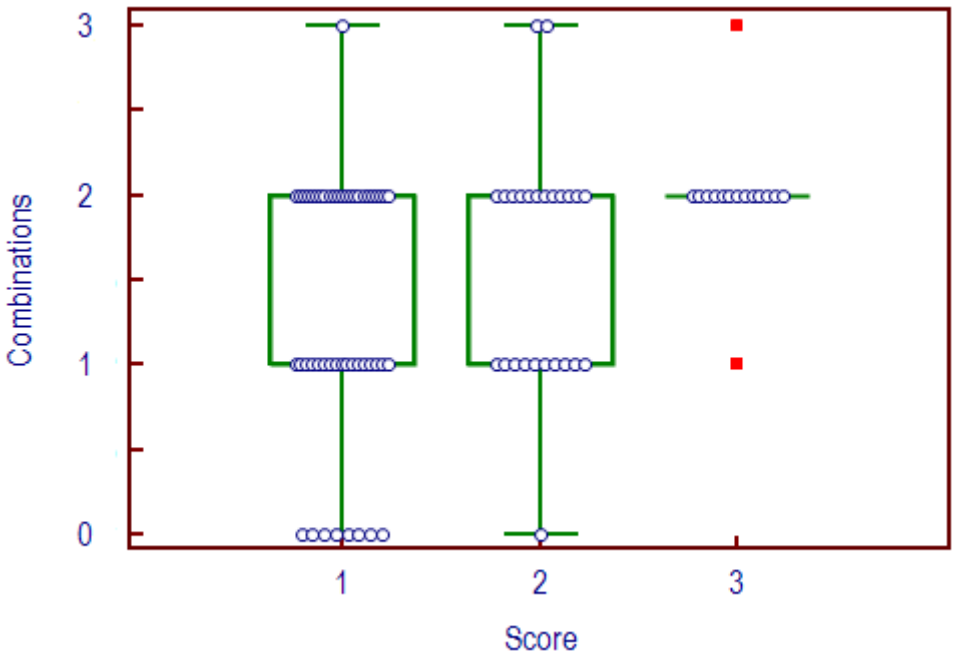

Figure 8. Correlation between various combinations of symptoms and clinical findings and the newly proposed probability scoring tool: 0 – normal clinical finding and no comorbidities, 1 – prolonged coughing with oropharyngeal injection and/or posterior laryngitis, 2 – asthma and posterior laryngitis alongside oropharyngeal wall redness, 3 – isolated hoarseness and/or chest pain with any clinical finding (Kruskal-Wallis test, p=0.0086, n=89).