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Validated Clinical Score to Predict Gastroesophageal Reflux in Patients with Chronic Laryngeal Symptoms: COuGH RefluX

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Abstract

Background & Aims—Discerning whether laryngeal symptoms result from gastroesophageal reflux is clinically challenging and a reliable tool to stratify patients is needed. We aimed to develop and validate a model to predict likelihood of gastroesophageal reflux disease (GERD) among patients with chronic laryngeal symptoms.

Methods—This multicenter international study collected data from adults with chronic laryngeal symptoms that underwent objective testing (upper GI endoscopy and/or ambulatory reflux monitoring) between 3/2018–5/2023. The training phase identified a model with optimal receiver operating characteristic curves, and beta coefficients informed a weighted model. The validation phase assessed performance characteristics of the weighted model.

Results—856 adults, 304 in training cohort and 552 in the validation cohort, were included. In the training phase the optimal predictive model [AUC 0.68 (95% CI 0.62, 0.74)] - the COuGH RefluX score - consisted of **C**ough, **O**verweight/obesity, **G**lobus, **H**iatal Hernia, **R**egurgitation,

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and male se**X** with a lower threshold of 2.5 and upper threshold of 5.0 to predict proven GERD. In the validation phase, the COuGH RefluX score had an AUC of 0.67 (0.62, 0.71) with 79% sensitivity and 81% specificity for proven GERD.

Conclusions—The externally validated COuGH RefluX score is a clinically practical model to predict likelihood of proven GERD. The score classifies most patients with chronic laryngeal symptoms as low/high likelihood of proven GERD, with only 38% remaining as indeterminate. Thus, the COuGH RefluX score can guide diagnostic strategies and reduce inappropriate proton pump inhibitor use or testing for patients referred for evaluation of chronic laryngeal symptoms.

Keywords

Laryngopharyngeal Reflux; Diagnosis; Esophageal pH Monitoring; Esophagus

Introduction

Patients experiencing chronic laryngeal symptoms such as voice hoarseness, sore throat, throat clearing, cough, and globus sensation[1–5] are often referred by their primary care physician to sub-specialists.[6,7] While multiple, non-reflux related conditions can cause laryngeal symptoms, laryngopharyngeal reflux (LPR) is reflexively implicated in 80% of cases.[2] LPR refers to the retrograde reflux of gastric contents to the larynx as a source of laryngeal symptoms. However, discerning whether laryngeal symptoms are a direct cause of gastroesophageal reflux disease (GERD) is challenging.[7] While empiric proton pump inhibitor (PPI) trials are commonly initiated,[8,9] laryngeal symptoms are poorly responsive to PPIs, and patients subsequently undergo further evaluation including on average 6 diagnostic tests.[6] Despite this arduous journey, the majority will not achieve symptom relief or diagnostic clarity,[6,10–12] leading to impaired psychosocial status, social functioning and well-being.[10,11,13] The cost of evaluation and management of chronic laryngeal symptoms is as high as $5,438/patient, equating to over $50 billion in annual health care costs.[6]

A reliable clinical tool to stratify the likelihood of proven GERD and thereby guide PPI utilization and diagnostic testing is critically needed. The objective of this study was to develop and validate a clinically practical model to predict the likelihood of GERD in the evaluation of chronic laryngeal symptoms.

Methods

Study Design and Subjects

This two-phase international multicenter study included adults with chronic laryngeal symptoms (throat clearing, mucus in throat, sore throat, dysphonia, cough, globus) who had undergone esophagogastroduodenoscopy (EGD) and/or ambulatory reflux monitoring (24h impedance-pH or prolonged wireless reflux monitoring). Exclusion criteria included prior foregut surgery. Further, patients without a conclusive diagnosis of no GERD or conclusive diagnosis of GERD (e.g., borderline endoscopic findings such as Los Angeles A esophagitis or short segment Barrett’s esophagus without confirmatory reflux monitoring data) were excluded. The Institutional Review Board at each center approved the study. Data Use Agreements were obtained with each center and de-identified data were provided

to the primary site University of California San Diego (UCSD). Data collected included demographic information, body mass index (BMI), symptom presentation, endoscopic findings, and ambulatory reflux monitoring. Symptoms were self-reported and physician determined based on questionnaires and clinic visits.

This two-phase study consisted of a training phase to develop the risk prediction score, followed by an external validation phase. In the training phase data were collected at a single center (primary site; UCSD) from 7/2019 – 1/2023. In the validation phase data were collected from five centers including four GERD referral centers across the US (UCSD [San Diego, CA], Brigham and Women's Hospital [Boston, MA], Northwestern University [Chicago, IL], and Washington University [St. Louis, MO]) and one Asian GERD referral center (Tzu Chi University [Hualien County, Taiwan]). The training and validation data from UCSD were separate. Validation data was collected from 3/2018 to 5/2023. External site study investigators were blind to the results from the training phase.

Outcomes and Definitions

Patients were categorized as proven or unproven GERD. Proven GERD was defined as LA Grades B/C/D esophagitis and/or long segment Barrett's esophagus (≥ 3 cm) on EGD, esophageal acid exposure time (AET) ≥6% and/or ≥80 reflux events/24h on ambulatory reflux monitoring off PPI[14,15], or AET ≥2% and/or ≥40 reflux events on impedance-pH on PPI.[16] Unproven GERD was defined as a negative ambulatory reflux monitoring study off PPI (AET <6% and/or <80 reflux events/24h). Patients with LA Grade A esophagitis, short-segment Barrett's esophagus, or a negative impedance-pH study on PPI, who did not have additional reflux testing off PPI therapy, were excluded from analyses due to the inability to conclusively exclude GERD. Hiatal hernia ≥1 cm in size was included as presence of a hiatal hernia and ascertained from EGD reports or high-resolution manometry, with the larger size being used.

Sample Size

The target *a priori* sample size goals were approximately 300 for the training cohort and 500 for the validation cohort. See supplemental materials for full details.

The validation cohort sample size was selected after identifying the area under the curve (AUC) of 0.69 for the constructed COuGH RefluX score. Considering validation often shows poorer performance (e.g., lower AUC values) and our desire to recruit a more generalizable external validation data set from 5 total sites, we considered a less optimistic AUC of 0.55 with LPR prevalence of 50% resulting in a target sample size of 500 for a 95% CI that still excludes 50%.

Statistical Analysis

Summaries are reported as frequency (percent) for categorical measures and mean (standard deviation) for continuous measures. Baseline comparisons use the chi-squared or Fisher's exact test for categorical variables and a two-sample t-test for continuous variables to compare between unproven and proven GERD groupings. Logistic regression models were used to estimate the unadjusted and adjusted models for identifying model performance with

the AUC estimated to summarize overall performance. Missing data were not imputed. Data were analyzed using R v4.2.0 (Vienna, Austria).

In the training phase univariate logistic regressions assessed association between clinical and demographic variables with proven versus unproven GERD. Variables included: Sex, BMI, GerdQ score, RSI score, regurgitation, dysphagia, chest pain, throat clearing, sore throat, dysphonia, cough, heartburn, globus, mucus in throat, inlet patch on EGD, stricture on EGD, hiatal hernia, gastro-esophageal valve hill grade, and pepsin. Variables with p-values of 0.30 or less were included in multiple logistic regression permutations. This threshold was selected to reduce the number of potential variables while recognizing that in multiple logistic regression models the observed univariate effect may change in magnitude and significance, while still potentially resulting in a meaningful prediction model. The variance inflation factors for our models were all <2 indicating that no variables were highly correlated, therefore multiple logistic regression provides the ability to account for the influence of these multiple predictors in the context of simultaneously adjusting for the contributions of all included variables. An optimal model was discriminated by receiver operating characteristic curves. Next, a weight model that can be implemented in the clinical setting was developed. Weights were chosen to approximate the multiple logistic regression beta coefficients and corresponding odds ratios by rounding to the 0.5 increments. The *a priori* goal for the weighted model was to identify risk prediction score cut-offs at lower threshold of less than 20% false negative rate and upper threshold of less than 20% false positive rate in order to optimize both sensitivity and specificity.

The validation phase examined the performance of the weighted risk prediction model across an external multi-center international validation cohort through receiver operator characteristics including AUC, sensitivity, specificity, false negative rate, false positive rate and negative predictive value.

Since the primary goal of this model was to optimize the negative predictive value in order to identify patients with chronic laryngeal symptoms that do not have GERD and should not receive PPI therapy or further evaluation with EGD/ambulatory reflux monitoring, a secondary analysis evaluated a risk prediction score with 10% or lower false negative rate (i.e., optimize sensitivity).

Additional post-hoc analyses were conducted. First, recognizing that data on hiatal hernia is not always available in clinical practice, post-hoc analyses excluded hiatal hernia as a variable in the risk prediction model. Further analyses were conducted to measure score performance, via the AUC, in patients with isolated laryngeal symptoms and in patients with concomitant laryngeal and esophageal symptoms in the entire cohort combined. Finally, sub-group analyses assessed distribution of scores among patients with an inconclusive range of AET (4 to 6%).

Results

A total of 856 patients are included in this study: 304 in the training cohort and 552 in the validation cohort.

Training Phase

The 304 patients in the training cohort had a mean age of 52.7 years (SD 16.6), mean BMI of 26.3 kg/m^2 (5.3), and 130 (43%) were male (Table 1). 141 (46%) met criteria for unproven GERD and 163 (54%) for proven GERD. Among those with proven GERD, proven GERD was identified in 15% on EGD, 79% on ambulatory reflux monitoring off PPI, and 17% on 24h impedance-pH on PPI. The proven GERD group, compared to unproven GERD, was older in age [55.1 (16.7) vs 49.8 (16.1), p<0.01], mostly male [78 (48%) vs 52 (37%), p=0.06], and with higher BMI [27.4 (5.8) vs 25.1 (4.6), p<0.01]. The proven GERD group had higher proportions with regurgitation [126 (77%) vs. 101 (72%) p=0.29] and cough [121 (74%) vs. 94 (67%), p=0.17], and lower proportions of globus [94 (58%) vs. 101 (72%), p=0.01] (Table 1).

A total of 18 multivariable regression models were evaluated. The optimal permutation had an AUC of 0.69 (0.63, 0.75) and included: **C**ough [OR 1.50 (95% CI 0.87, 2.60)]; **O**verweight [BMI 25–30 kg/m2, 1.62 (0.94, 2.82)]/**O**besity [BMI ≥ 30kg/m^2 1.99 (1.05, 3.83)]; **G**lobus [0.51 (0.30, 0.86)]; **H**iatal hernia [2.62 (1.56, 4.46)]; **R**egurgitation [1.42 (0.81, 2.51)]; male se**X** [1.70 (1.03, 2.83)] (Table 2).

A weighted risk prediction model was developed referred to as the **COuGH RefluX** score: **C**ough: 1.5 points; **O**verweight: 1.5 points/**O**besity 2.0 points; **G**lobus: −1.0 point; **H**iatal hernia: 2.5 points; **R**egurgitation: 1.5 points; male se**X**: 1.5 points with total COuGH RefluX scores ranging from −1.0 to 9 (Figure 1). The AUC of the weighted COuGH RefluX score was 0.68 (0.62, 0.74) (Figure 2). A lower threshold of 2.5 was 82% (75%, 88%) sensitive for proven GERD and a score of ≥ 5 was 79% (71%, 85%) specific for proven GERD (Figure 2). Among the training cohort, 27% had scores of ≤ 2.5 and 34% had scores of ≥ 5, with 39% remaining in the middle, indeterminate category.

Validation Phase

The 552 patients in the validation cohort were a mean age of 53.2 years (SD 15.1), mean BMI of 27.0 kg/m^2 (6.7), and 196 (36%) were male. 370 (67%) met criteria for unproven GERD and 182 (33%) for proven GERD (Table 3). Of those with proven GERD, proven GERD was found in 24% on EGD, 90% on ambulatory reflux monitoring off PPI, and 3% on 24h impedance-pH on PPI. Among the validation cohort, the weighted COuGH RefluX score had an AUC of 0.67 (0.62, 0.71) (Figure 2). A score of > 2.5 was 79% sensitive (72%, 84%) and a score of ≥5 was 81% specific (76%, 84%) for predicting proven GERD (Figure 2). Among the validation cohort, 35% had scores of ≤2.5 and 27% had scores of ≥5, with 38% remaining in the middle, indeterminate category. Of 163 subjects in the ≤2.5 group with EGD data available, 3 (2%) had severe erosive disease (LA C/D esophagitis).

Sensitivity Analyses to Optimize Negative Predictive Value of COuGH RefluX Score

In the training cohort, a COuGH RefluX score of ≤1.5 met criteria for a false negative rate less than 10% and increased sensitivity to 93% (87%, 96%) for proven GERD. This lower threshold of 1.5 performed similarly in the validation cohort with a sensitivity of 92% (87%, 95%) for proven GERD. In the training cohort, 37 (12%) had scores of ≤1.5 and in the validation cohort, 111 (20%) had scores of had scores of ≤1.5.

Post-hoc Analyses Excluding Hiatal Hernia

In the training cohort, the weighted model excluding hiatal hernia from the original score had an AUC of 0.63 (0.57, 0.70), with scores ranging from −1.0 to 8.0. The weighted scores included the following point allocations: Cough: 1.5 points; Overweight: 1.5 points/Obesity 2.0 points; Globus: −1.0 point; Regurgitation: 1.5 points; male se**X**: 1.5 points. A lower threshold of 1.5 was 87% sensitive (81%, 92%) for proven GERD and a higher threshold of 4.5 was 83% specific (76%, 89%) for proven GERD. In the validation cohort this weighted model excluding hiatal hernia had an AUC of 0.65 (0.60, 0.69) where a score of 1.5 was 87% (82%, 92%) sensitive and a score of 4.5 was 85% (81%, 89%) specific for proven GERD (Figure 2). In this model, 26% had scores of ≤ 1.5, 18% had scores of ≥ 4.5, and 56% were in the middle, indeterminate range.

Post-hoc Analysis Evaluating Acid Exposure Time of 4 to 6%

According to Lyon consensus 2.0 an acid exposure time of 4 to 6% is inconclusive for GERD.[15] In this study, 95 patients in total had an acid exposure time off acid suppression of 4 to 6%. Among this group 19 (20%) had a low COuGH RefluX score (≤2.5), 40 (42%) had an indeterminate score (2.5 to 4.5) and 36 (38%) had a high score (≥5.0).

Post-hoc Analyses: Isolated Laryngeal Symptoms vs Laryngeal & Esophageal Symptoms

Among the 720 patients with esophageal and laryngeal symptoms the AUC of the COuGH RefluX score was 0.69 (0.65, 0.73) for predicting proven GERD and among the 136 patients with isolated laryngeal symptoms the AUC was 0.61 (0.52, 0.71) for predicting proven GERD (Table 4).

Discussion

The COuGH RefluX score is an externally and internationally validated clinically practical model to predict the likelihood of proven GERD in adults with chronic laryngeal symptoms using widely available clinical data: symptoms, BMI, sex, and presence of a hiatal hernia. Though information on hiatal hernia is often available via imaging studies or prior EGD, a modified score excluding hiatal hernia when data is not available, does not compromise the predictive ability of the score. The COuGH RefluX score is 79% sensitive and 81% specific for proven GERD and categorizes 35% as low risk of GERD, for whom further diagnostic testing or a PPI trial may not be needed, and 27% as high risk for GERD in whom upfront reflux testing may be unnecessary. Thus, utilization of the COuGH RefluX score has potential to reduce testing in more than 60% of patients undergoing evaluation for LPR.

The clinical implications of the COuGH RefluX score in practice are significant. Currently, most patients undergo ineffective PPI trials despite guidelines recommending upfront diagnostic testing in patients with chronic laryngeal symptoms. Practical shortcomings which limit widespread use of upfront diagnostic testing include the high cost and resources needed to implement this strategy, given the prevalence of chronic laryngeal symptoms.[7,14,17,18] Additionally, primary care settings do not have ready access to upfront diagnostic testing, and further, patients are often reluctant to undergo invasive testing (EGD/reflux monitoring) in lieu of trailing PPIs. In these settings, the COuGH RefluX stratifies

patients as unlikely to have GERD (COuGH RefluX ≤2.5), likely to have GERD (COuGH RefluX ≥5) and indeterminate for GERD (COuGH RefluX 3.0–4.5) (Figure 1). When the likelihood of GERD is high (COuGH RefluX ≥5) next steps could include a PPI trial, without requiring upfront GERD testing. On the other hand, in patients with a low likelihood of GERD (COuGH RefluX ≤2.5 (or ≤1.5 to optimize sensitivity) non-reflux targeted therapy could be pursued, rather than empiric PPI trials or further testing. Only the indeterminate category would potentially require upfront objective testing, ensuring appropriate utilization of limited resources and thus tremendously reducing costs. However, physiologic testing to confirm the presence of GERD is recommended prior to invasive management.[7]

A multicenter study that laid the groundwork for the COuGH RefluX score examined 302 patients with chronic laryngeal symptoms and identified five distinct clinico-physiologic phenotypic groups with varying symptom presentation, clinical features, and physiologic metrics.[19] This study confirmed that patients with chronic laryngeal symptoms present a heterogeneous group with varied mechanisms of disease and symptom presentations that are not always related to GERD, highlighting the potential of a clinically practical score inclusive of symptoms and clinical features to identify which patients are likely or unlikely to have proven GERD. The current study reinforces these initial concepts, especially the fact that the term ‘LPR’ should not be used based on symptom presentation alone. The COuGH RefluX score fulfills this important need by stratifying likelihood of GERD using simple clinical and demographic data commonly accessible to clinicians.

There has been limited research in risk prediction modeling to determine the likelihood of abnormal acid exposure in patients with chronic laryngeal symptoms. Patel *et al.* evaluated 471 patients with refractory heartburn or suspected extra-esophageal reflux symptoms who failed a PPI trial and developed the HAs-BEER score (Heartburn, Asthma, and BMI > 25 in extra-esophageal reflux), which recommends reflux testing off PPI for individuals with a low score, reserving impedance-pH monitoring on PPI for individuals with a high score.[20] In another study, of 124 patients presenting with chronic laryngeal symptoms, the Horvath Score was developed which included point allocation for the Reflux Symptom Index (RSI), Reflux Finding Score (RFS), transnasal esophagoscopy and results from oropharyngeal pH monitoring to determine the severity of LPR versus no LPR.[21] These studies were clinically intriguing; however, current guidance recommends that on PPI testing be reserved for patients with prior evidence of conclusive GERD[22] and oropharyngeal pH monitoring is not currently recommended in evaluation of chronic laryngeal symptoms.[7,23] The COuGH RefluX score represents an updated and easy to calculate risk prediction score that could be adopted into medical practice to help predict the likelihood of GERD and guide next steps in the diagnosis of these patients.

Myriad non-reflux related disease processes can drive laryngeal symptoms, including cognitive processes such as anxiety, perseveration and behavioral disorders.[24] Prior studies have demonstrated high levels of hypervigilance and anxiety across patients with chronic laryngeal symptoms.[25] In our study, globus sensation was a negative predictor of GERD, suggesting that globus is more likely related to hypersensitivity and hypervigilance rather than reflux pathophysiology.[7] Globus is the sensation of a lump in the throat, when not consuming foods/liquids, which is differentiated from dysphagia (difficulty

swallowing foods/liquids). Therefore, while the COuGH RefluX score can predict likelihood of abnormal esophageal reflux burden in a patient with laryngeal symptoms, alternate mechanisms of symptom generation remain possible, and adjunctive therapeutic options beyond reflux management (e.g., voice and behavioral therapy) are important in the management armamentarium.

Our study has several strengths. The robust sample size and validation of data across multiple centers highlights reproducibility and generalizability of the COuGH RefluX score. Further, the score is simple and easy to implement across health care systems, with potential for online availability as a risk calculator. These strengths are tempered by a few limitations, including those that are inherent with retrospective observational data. While data comes from tertiary care high volume centers which may limit generalizability, the study was designed to capture practice patterns and populations across regions in the United States as well internationally. Notably, history of PPI use or response to PPI, prior workup for laryngeal symptoms, nor treatment outcomes were assessed, which limits the characterization of the baseline population as well as ability to manage these complex patients. In addition, the cohort of patients with isolated laryngeal symptoms was small and thus underpowered to develop a model for this sub-group alone. Importantly, this study developed and validated the COuGH RefluX score against the well-established physiomarker of acid exposure. These results represent a novel first-line approach to evaluation of these patients and lays the foundation for future, critically needed, outcomes studies to assess the prognostic role of the COuGH RefluX score.

In conclusion, the COuGH RefluX score is a simple, objective validated score that categorizes most patients with chronic laryngeal symptoms as low/high likelihood of GERD utilizing widely available clinical data. The score can be used, in conjunction with other non-invasive testing, to help guide diagnostic strategies to reduce inappropriate PPI use and testing for patients referred for LPR evaluation. Future studies are needed to understand how the COuGH RefluX score predicts treatment outcomes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data Sharing Statement:

Data, analytic methods, and study materials will be made available to other researchers by request whose used of the proposed data has been approved. Data is available on request to mgreytak@health.ucsd.edu.

Abbreviations:

AET	Acid exposure time
AUC	Area under the curve
BMI	Body mass index
CI	Confidence interval
EGD	Esophagogastroduodenoscopy
GERD	Gastro-esophageal reflux disease
LPR	Laryngopharyngeal reflux
MAPE	Mean absolute error in predicted probabilities
PPI	Proton pump inhibitor
UCSD	University of California San Diego

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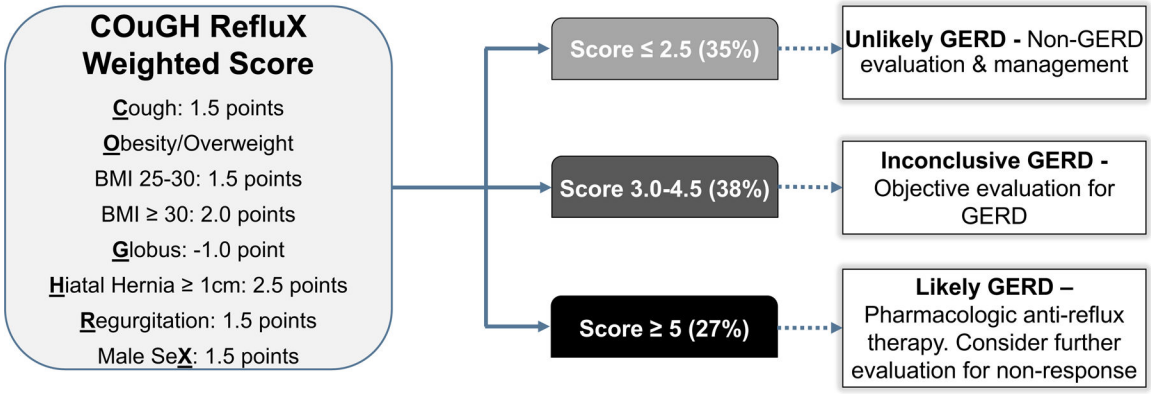

Figure 1:

Weighted COuGH RefluX Score with a lower threshold of 2.5 and upper threshold of 5. Among the validation cohort, 35% had scores of ≤2.5, 27% had scores of ≥5, and 38% fell into the middle category. For patients with low scores, consider non-reflux targeted therapy, as these patients are unlikely to have GERD. For patients with high scores, consider lifestyle and pharmacologic reflux targeted therapies. For patients in the inconclusive category, consider objective GERD evaluation. In patients being evaluated for invasive management, physiologic testing is needed.

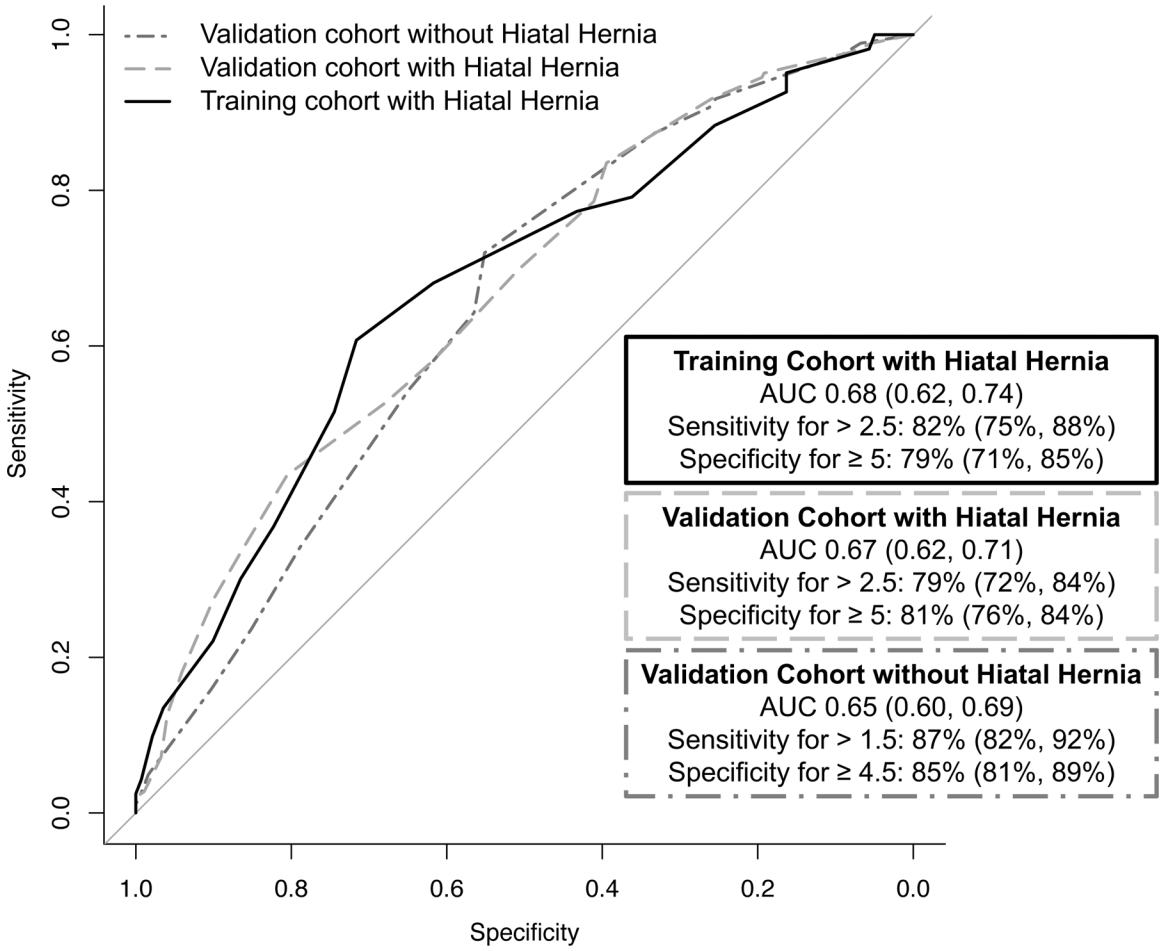

Figure 2:

Receiver Operating Curves for COuGH RefluX Score. The training cohort is identified via the black line and the validation cohort via the light grey dotted line. Since hiatal hernia is not always clinically available, a model excluding hiatal hernia, as demonstrated by the dark grey dotted line, is also shown.

Table 1:

Baseline Characteristics Training Cohort; Univariate Analysis

	Overall (n=304)	Unproven GERD (n=141)	Proven GERD (n=163)	P-value
Demographics				
Male Sex	130 (43%)	52 (37%)	78 (48%)	0.06
Age (years)	52.7 (16.6)	49.8 (16.1)	55.1 (16.7)	<0.01
Body Mass Index (kg/m^2)	26.3 (5.3)	25.1 (4.6)	27.4 (5.8)	<0.01
Esophageal Symptoms				
Heartburn	221 (73%)	100 (71%)	121 (74%)	0.52
Regurgitation	227 (75%)	101 (72%)	126 (77%)	0.29
Chest Pain	166 (55%)	80 (57%)	86 (53%)	0.49
Laryngeal Symptoms				
Throat Clearing	227 (75%)	107 (76%)	120 (74%)	0.69
Sore Throat	81 (27%)	38 (27%)	43 (26%)	1.00
Voice Hoarseness	175 (58%)	78 (55%)	97 (60%)	0.49
Cough	215 (71%)	94 (67%)	121 (74%)	0.17
Globus	195 (64%)	101 (72%)	94 (58%)	0.01
Mucus in Throat	207 (68%)	102 (72%)	105 (64%)	0.18
Endoscopic Findings				
Erosive Esophagitis	44/259 (17%)	8/119 (7%)	36/140 (26%)	<0.01
Los Angeles A	25/259 (10%)	8/119 (7%)	17/140 (12%)	0.21
Los Angeles B	11/259 (4%)	0/119 (0%)	11/140 (8%)	<0.01
Los Angeles C	6/259 (2%)	0/119 (0%)	6/140 (4%)	0.03
Los Angeles D	2/259 (1%)	0/119 (0%)	2/140 (1%)	0.50
Barrett's Esophagus	12/259 (5%)	0/119 (0%)	12/140 (9%)	<0.01
Hiatal Hernia	103 (34%)	33 (23%)	70 (43%)	<0.01
Ambulatory Reflux Findings				
Mean acid exposure time 24h impedance-pH on/off PPI (n=151)	3.6 (4.4)	1.5 (1.4)	5.7 (5.3)	<0.01
Mean number of reflux events 24h impedance-pH on/off PPI (n=150)	60.0 (48.8)	34.1 (20.5)	87.3 (54.8)	<0.01
Mean acid exposure time prolonged wireless reflux monitoring off PPI (n=161)	6.5 (4.7)	2.6 (1.9)	9.6 (3.9)	<0.01

Table 2:

Optimal Model in Training Cohort; Multivariable Regression Model

Predictor	OR	95% CI	P-value
Cough	1.50	0.87, 2.60	0.15
Overweight/**O**besity			
BMI 25–30 kg/m^2	1.62	0.94, 2.82	0.09
BMI ≥ 30kg/m^2	1.99	1.05, 3.83	0.04
Globus	0.51	0.30, 0.86	0.01
Hiatal Hernia	2.62	1.56, 4.46	<0.01
Regurgitation	1.42	0.81, 2.51	0.23
se**X** (Male)	1.70	1.03, 2.83	0.04

Table 3:

Baseline Characteristics, Validation Cohort; Univariate Analysis

	Overall (n=552)	Unproven GERD (n=370)	Proven GERD (n=182)	P-value
Demographics				
Male Sex	196 (36%)	122 (33%)	74 (41%)	0.09
Age (years)	53.2 (15.1)	52.8 (15.1)	53.9 (15.2)	0.45
Body Mass Index (kg/m^2)	27.0 (6.7)	25.7 (5.9)	29.5 (7.4)	<0.01
Esophageal Symptoms				
Heartburn	369 (67%)	231 (62%)	138 (76%)	<0.01
Regurgitation	305 (55%)	192 (52%)	113 (62%)	0.03
Chest Pain	179 (32%)	117 (32%)	62 (34%)	0.56
Laryngeal Symptoms				
Throat Clearing	355 (64%)	250 (68%)	105 (58%)	0.02
Sore Throat	147 (27%)	116 (31%)	31 (17%)	<0.01
Voice Hoarseness	301 (55%)	208 (56%)	93 (51%)	0.28
Cough	351 (64%)	231 (62%)	120 (66%)	0.45
Globus	364 (66%)	252 (68%)	112 (62%)	0.13
Mucus in Throat	339 (61%)	243 (66%)	96 (53%)	<0.01
Endoscopic Findings				
Erosive Esophagitis	85/450 (19%)	22/283 (8%)	63/167 (38%)	<0.01
Los Angeles A	45/450 (10%)	22/283 (8%)	23/167 (14%)	0.05
Los Angeles B	30/450 (7%)	0/283 (0%)	30/167 (18%)	<0.01
Los Angeles C	5/450 (1%)	0/283 (0%)	5/167 (3%)	<0.01
Los Angeles D	5/450 (1%)	0/283 (0%)	5/167 (3%)	<0.01
Barrett's Esophagus	15/448 (3%)	5/281 (2%)	10/167 (6%)	0.03
Hiatal Hernia	195 (35%)	111 (30%)	84 (46%)	<0.01
Ambulatory Reflux Findings*				
Mean acid exposure time 24h impedance-pH on/off PPI (n=422)	3.6 (5.5)	1.5 (1.5)	8.8 (7.8)	<0.01
Mean number of reflux events 24h impedance-pH on/off PPI (n=422)	49.9 (54.0)	33.6 (19.5)	89.2 (82.9)	<0.01
Mean acid exposure time prolonged wireless reflux monitoring off PPI (n=139)	6.2 (5.1)	2.7 (1.6)	10.4 (4.5)	<0.01

Table 4:

Characteristics of Entire Cohort Isolated Laryngeal versus Concomitant Esophageal Symptoms

	Isolated Laryngeal Symptoms (n=136)	Laryngeal and Esophageal Symptoms (n=720)	P-value
Demographics			
Male Sex	63 (46%)	263 (37%)	0.03
Age (years)	55.5 (15.1)	52.5 (15.7)	0.04
Body Mass Index (kg/m^2)	26.3 (5.4)	26.8 (6.4)	0.41
Symptoms			
Heartburn	0 (0%)	590 (82%)	<0.01
Regurgitation	0 (0%)	532 (74%)	<0.01
Chest Pain	0 (0%)	345 (48%)	<0.01
Laryngeal Symptoms			
Throat Clearing	81 (60%)	501 (70%)	0.03
Sore Throat	30 (22%)	198 (28%)	0.21
Voice Hoarseness	47 (35%)	429 (60%)	<0.01
Cough	80 (59%)	486 (68%)	0.06
Globus	71 (52%)	488 (68%)	<0.01
Physiologic Measures			
Proven GERD	46 (34%)	299 (42%)	0.09
Erosive Esophagitis	18/102 (13%)	111/607 (18%)	1.00
Los Angeles A	11/102 (11%)	59/607 (10%)	0.72
Los Angeles B	3/102 (3%)	38/607 (6%)	0.25
Los Angeles C	3/102 (3%)	8/607 (1%)	0.20
Los Angeles D	1/102 (1%)	6/607 (1%)	1.00
Barrett's Esophagus	9/102 (9%)	18/605 (3%)	<0.01
Hiatal Hernia	42 (31%)	256 (36%)	0.33
Mean acid exposure time 24h impedance-pH on/off PPI	3.0 (5.7) n=109	3.8 (5.1) n=464	0.15
Mean number of reflux events 24h impedance-pH on/off PPI	49.0 (38.8) n=108	53.4 (55.6) n=464	0.44
Mean acid exposure time prolonged wireless reflux monitoring off PPI	5.8 (3.6) n=23	6.4 (5.0) n=277	0.56