Gastroesophageal Reflux in Children With Idiopathic Bronchiectases: a Pilot Study

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Research

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Abstract

Background:

The role of gastroesophageal reflux in bronchiectasis development is still object of discussion. We aimed to characterize gastroesophageal reflux (GER) in children with idiopathic bronchiectases (BC) and to analyse the relation with a morpho-functional High-Resolution Computed Tomography (HRCT) scoring system

Methods:

Multiple esophageal impedance-pH (MII-pH) parameters in children with respiratory symptoms with and without BC were compared. In children with BC spirometry was performed and HRCT score was calculated by evaluating in each lung lobe: 1.bronchiectasis-peribronchial wall thickening, 2.mucous plugging, 3.abscess-sacculations, 4.consolidations, 5.others. HRCT score was related to MII-pH results. HRCT score accuracy in predicting pathological MII-pH was evaluated by ROC curve.

Results:

20 children with BC and 20 without BC were enrolled. No significant differences were found in any MII-pH parameter between the two groups.

Among BC children, 7/20 had a pathological MII-pH and didn't show difference in respiratory function compared to those without GER.

There were no significant correlation between HRCT score and MII-pH parameters but a direct (not significant) correlation with RI (r=0.240 p=0.307), acid refluxes (r=0.022 p=0.925) and SI/SAP (r=0.041 p=0.865). The mean value of the HRCT score in children with BC with pathological MII-pH was higher than in the ones with normal MII-pH (6.571 vs. 4.846, p=0.0929). The Area Under the Curve was 0.736. A HRCT score of 4.5 and 7.5 were associated with a negative predictive value of 86.5% and a positive predictive value of 75% respectively.

Conclusions:

Children with idiopathic BC had no distinct GER features. HRCT scoring system showed a moderate accuracy in predicting MII-pH results and a value ≤4.5 is rarely associated with a pathological MII-pH.

Level of evidence:

not properly applicable as it is a non-interventional diagnostic evaluation study.

1. Background

Bronchiectases (BC) are a chronic pulmonary condition characterized by permanently dilated airways [1]. BC are uncommon in pediatric ages, with prevalence ranges, in European countries, from 67 to 362 per 100,000 individuals. However, affected patients present poor quality of life and comorbidities, that are related with the progression of the disease [1–4].

Cystic fibrosis is the main underlying disease, but BC may be consequent to other disorders [1]. Diagnosis of BC is currently made through High Resolution Computed Tomography (HRCT) which is considered the gold standard investigation and the only reliable imaging test for the assessment of morphological changes of the lung parenchyma [5].

The pathogenesis of BC is complex and not well defined [3]. The most recognized hypothesis is described by Cole's vicious cycle: an initial event compromises mucociliary clearance leading to chronic airway inflammation and progressive structural damage of the respiratory tract [3]. Different triggers have been considered and included: infections, immunodeficiencies, genetic diseases or aspiration of gastrointestinal content [6].

The latter has been attributed to gastroesophageal reflux (GER) and GER may cause BC by microaspirations into the tracheobronchial tree and respiratory symptoms by vagally-mediated reflex bronchoconstriction [7, 8]. The interaction between BC and GER is difficult to ascertain and GER disease (GERD) is frequently perceived as a risk factor that can exacerbate the underlying lung disease [7].

In children, the diagnosis of GERD is challenging due to clinical and technical confounding factors, inter-observer variability, unclear report of symptoms, lack of specific pediatric symptoms and questionnaires/scores, and of a gold standard diagnostic investigation. Currently, combined multichannel intraluminal impedance with pH monitoring (MII-pH) is considered the tool which best identifies, defines and quantifies both acid and non-acid GER and symptoms association [7, 9, 10].

In this pilot study we aimed to: 1) characterize GER assessed by MII-pH, in children with idiopathic BC; 2) assess the relation between GER and respiratory function through spirometry; 3) assess the accuracy of a morpho-functional HRCT scoring system in predicting MII-pH results .

2. Methods

All children submitted to MII-pH, from July 2014 to May 2019, because of chronic respiratory symptoms and/or BC were prospectively enrolled.

Inclusion criteria were all of the followings: age 0–18 years; persisting unexplained respiratory symptoms, such as dysphonia, nonproductive chronic cough, hoarseness, apnea/desaturations, apparent life-threatening episodes and/or BC confirmed by HRCT; informed consent signed by parents.

Children were excluded if: age ≥ 18 years; diagnosis of cystic fibrosis or ciliary dyskinesia or immune deficiency; esophageal or congenital chest malformation or previous gastrointestinal surgical

intervention; current fever or acute infection; ongoing or recent (one week) antibiotic treatment; acid inhibitors or other GER treatment started before MII-pH or HRCT; absence of parental consent.

Children with and without BC were matched for age and sex.

2.1. MII-pH monitoring

All children underwent 24-hour MII-pH monitoring using the same MII-pH ambulatory system (Sandhill device, Bioview Software). Disposable catheters, with a diameter of 1.5-2 mm and different lengths according to patient's height: <15 cm, 15–18 cm or > 18 cm respectively in infants < 75 cm, children 75–150 cm or > 150 cm, were used [10]. Each catheter had two antimony pH sensors and six impedance electrodes, 1.5-2 cm apart, in infants or children probe. The pH-electrode was calibrated using buffer solutions with pH 4.0 and 7.0, according to manufacturer's instructions. The catheter was positioned transnasally and pH electrode was placed at the second vertebra above the diaphragmatic angle. Probe position was estimated by Strobel formula (0.252 x body length + 5) and then confirmed by chest X-Ray [10]. The MII-pH monitoring had to last at least 18 hours without artifacts to meet eligibility criteria. The patients were encouraged to conduct normal daily activities with no dietary restriction except extremely hot/ice-cold/acid foods and drinks and carbonated beverages. Meal times, body position and timing of symptoms were recorded both automatically, by a portable digital data recorder, and manually, by a symptoms-diary.

In each patient GER and MII-pH parameters were recorded, classified and analyzed as previously reported [10–12].

The tracing analysis was first automatically analysed by a dedicated Sandhill software and then manually reviewed by a pediatric gastroenterologist with expertise in MII-pH.

The following parameters were evaluated: reflux index (RI), number of acid refluxes, total number of bolus refluxes (TNR), acid TNR (A TNR), weakly acidic TNR (WA TNR), alkaline TNR (Al TNR), proximal refluxes (PR), symptom index (SI) and symptom association probability (SAP). A summary of MII-pH parameters and definitions is reported in Table 1.

Table 1
MII-pH-parameters and clinical significance.

Acronym	Parameter	Significance	pathological values
TNR	Total number of reflux episodes	total number of acid, weakly acidic or non acid impedence (at least 2 distal channels) refluxes	> 70/24 hours in patients ages 1 year or older >100/24 hours in those younger than 1 year
RI	Reflux index	percentage of time of esophageal acid reflux (pH < 4)	≥ 5% pathological
SI	Symptom index	percentage of GER-associated symptoms among the total number of symptoms	≥ 50% pathological
SAP	Symptom association probability	Correlation (Fisher exact test) between number of intervals (2 minutes) with GER and symptom, number of intervals with GER and no symptom, number of intervals with symptom but no GER, and number of intervals without GER and symptom.	≥ 95% pathological

MII-pH was considered pathological when RI was ≥ 5% or when the TNR episodes were ≥ 70 in children older than 1 year or ≥ 100/24hours in infants, or when a significant association occurred between respiratory symptoms and reflux, based on SI (> 50%) or SAP (> 95%). Time window between reflux and symptoms for the automatic analysis was set at 2 minutes [9, 10]. Analysis of MII-pH tracings was performed blind to the HRCT score.

2.2. Imaging evaluation

HRCT images were reviewed by an experienced pediatric radiologist. A morpho-functional scoring system (modified by Eichinger M.) was used to evaluate BC extent [5, 13].

HRCT score was calculated by evaluating 5 morphological features in each lung lobe:

- Bronchiectasis/bronchial wall thickening
- Mucus plugging
- Abscess/sacculations
- Consolidation
- Special findings (e.g. pleural effusion, pleural reaction or pneumothorax)

For each parameter, a semi-quantitative score from 0 to 2 was assigned (0 = no abnormality, 1 = < 50% of the lobe involved, 2 = ≥ 50% of the lobe involved). The maximum score per lobe was 10 and the maximum score per patient was 60. Analysis of HRCT score was performed blind to MII-pH results.

2.3. Spirometry

All children with BC underwent a basal spirometry and the following parameters were evaluated: forced vital capacity (FVC), forced expiratory volume in one second (FEV1), FEV1/FVC and forced expiratory flow 25/75%.

2.4. Statistical analysis

All data were analyzed using Prism 8 statistical software. Mean and standard deviation were calculated. T-test or Mann Whitney test were used to compare the characteristics of GER and MII-pH parameters in children with or without BC. T-test was also used to compare spirometry results in children with BC with and without pathological MII-pH. Spirometry values were described as z-score, calculated by using the Global Lung Function Initiative 2012 equation.

HRCT score in children with BC was correlated to RI, TNR, A TNR, WA TNR, Al TNR and PR by Spearman test. HRCT scoring system results were compared in children with BC with or without pathological MII-pH. sensitivity, specificity, positive (PPV) and negative (NPV) predictive values of HRCT score were also calculated and HRCT score accuracy in predicting pathological MII-pH was evaluated by ROC curve.

P-value < 0.05 was considered statistically significant.

2.5. Ethics

Research was conducted in accordance with the Declaration of Helsinki (as revised in Fortaleza, Brazil, October 2013). Design and aims of the study were fully explained to all participant parents and informed consent was obtained before performing investigations.

3. Results

3.1. Population and clinical findings

40 children were included: 20 with BC (mean age 99.00 ± 59 months, 12 males) and 20 without BC (mean age 97.00 ± 61 months p: 0.2918, 15 males p: 0.1577).

The symptoms reported in children with BC were: recurrent respiratory infections (in 17/20), chronic productive cough (in 2/20), and croup (in only one child).

The most frequently reported respiratory symptom in children without BC was chronic non-productive cough (in 10/20, 50%, of children). In addition, laryngospasm, hoarseness, episodes of apnea, dysphonia, laryngitis, pharyngeal globe were reported (each symptom in 2/20 children), and/or posterior rhinorrhea,

stridor, drooling and snore (each recorded in one patient). In both groups all patients reported more than one respiratory symptom.

Gastrointestinal symptoms (vomit, heartburn, restrosternal and abdominal pain) were also complained by 10/20 patients with BC and 8/20 children without BC (p:0.05372).

3.2. MII-pH results

MII-pH was pathological in 7 (35%) patients with BC and in 8 (40%) children without BC. In particular, 4/7 patients with BC and 6/8 children without BC showed a significant association (positive SI or SAP) between respiratory symptoms and GER; 4/7 patients with BC and 4/8 children without BC had a pathological RI. No significant difference was found between the two groups of children (Table 2).

Table 2

Mean (standard deviation) of each MII-pH† parameter in children with bronchiectases and without bronchiectases.

Group	**Bronchiectasis**	**Without Bronchiectases**	***p-value***
No. children	**(N = 20)**	**(N = 20)**	
MII-pH† parameter	**Mean (SD‡)**	**Mean (SD‡)**	
RI§%	4.4 (5.3)	4.1 (5.2)	*0.883*
TNR˙	44 (37)	48 (25)	*0.7*
A TNR¥	25 (27)	32 (24)	*0.3685*
WA TNR¤	18 (21)	13 (9.7)	*0.397*
Al TNR˚	1.3 (1.9)	2.3 (5.4)	*0.4406*
PR▯	27 (27)	18 (13)	*0.2093*

†MII-pH = pH-impedance, ‡SD = Standard Deviation, §RI = Reflux Index, ˙TNR = Total Number Of Impedance Refluxes, ¥A TNR = Acid TNR, ¤WA TNR = Weakly Acidic TNR, ˚Al TNR = Alkaline TNR, ▯PR = Proximal Refluxes.

Mean and standard deviation of MII-pH results in children with BC are showed in Table 3. As expected, in children with pathological MII-pH there were a significant higher RI and number of acid refluxes.

Gastrointestinal symptoms were reported in 3/7 (42.85%) and in 7/13 (53.8%) children with BC, with and without pathological MII-pH respectively (p-value 0.66).

Table 3

MII-pH† results in children with bronchiectases with and without pathological MII-pH† (mean ± SD‡).

MII-pH† parameter	Normal MII-pH† (N = 7)	Pathological MII-pH† (N = 13)	*p-values*
RI§%	1.92 ± 1.58	8.91 ± 6.86	*0.0022*
TNR	34.15 ± 18.61	62.00 ± 54.71	*0.1074*
A TNR˙	23.23 ± 19.43	33.29 ± 40.47	*0.4574*
WA TNR¥	13.15 ± 8.02	27.71 ± 33.31	*0.1437*
Al TNR¤	1.38 ± 2.33	1.00 ± 1.00	*0.6846*
Acid reflux	25.00 ± 18.96	88.43 ± 95.36	*0.0294*
PR˚	18.92 ± 14.07	41.00 ± 38.84	*0.0780*

†MII-pH = pH-impedance, ‡SD = Standard Deviation, §RI = Reflux Index, TNR = Total Number Of Impedance Refluxes, ˙A TNR = Acid TNR, ¥WA TNR = Weakly Acidic TNR, ¤Al TNR = Alkaline TNR, ˚PR = Proximal Refluxes.

3.3 Spirometry

Spirometry was successfully performed in 17/20 children with BC, in particular 5/17 (29.4%) had a pathological MII-pH. Children with pathological or normal MII-pH did not shown significant difference in any respiratory score (Table 4.).

Table 4

Comparison between FVC†, FEV-1‡, FEV1/FVC, MMEF 75/25§ z-score in children with bronchiectases with pathological and normal MII-pH¶.

	Mean (Standard Deviation)		*p-value*
	Pathological MII-pH¶ (N = 7)	Normal MII-pH¶ (N = 13)	
FVC† z-score	-1.14 (1.19)	-0.92 (1.06)	*0.7226*
FEV1‡ z-score	-1.28 (1.58)	-1.36 (1.12)	*0.9015*
FEV1/FVC z-score	-0.38 (1.03)	-0.82 (1.15)	*0.4752*
MMEF 75/25§ z-score	-1.27 (1.26)	-1.54 (1.14)	*0.6695*

[†]FVC = forced vital capacity, [‡]FEV1 = forced expiratory volume in one second, [§]MMEF 75/25 = forced expiratory flow 25/75%, [¶]MII-pH = esophageal pH-impedance.

3.4. HRCT scoring system and GER

HRCT score in patients with BC ranged from 2 to 10 with a mean value of 5.45.

The mean value of HRCT score in children with a pathological or normal MII-pH was 6.571 and 4.846 respectively (p:0.0929).

There was no distinct lobe involvement or HRCT characteristic in children with pathological or normal MII-pH (Table 5); the lower and middle right lung lobes were affected by BC in 6 children with pathological MII-pH and in 9 children with normal MII-pH (p:0.412).

Table 5

Mean ± SD[‡] of single parameters of HRCT[†] score in bronchiectases children with normal and pathological pH-impedance.

	Bronchiectasis (m[¶] ± SD[‡])	**Mucus plugging (m[¶] ± SD[‡])**	**Abscess/sacculations (m[¶] ± SD[‡])**	**Consolidation (m[¶] ± SD[‡])**	**Special findings (m[¶] ± SD[‡])**
Normal MII-pH[§] (N = 13)	1.69 ± 0.947	0.69 ± 0.751	0.08 ± 0.277	1.85 ± 0.689	0.54 ± 0.776
Pathological MII-pH[§] (N = 7)	2 ± 0.816	0.71 ± 0.951	0.29 ± 0.756	2.57 ± 1.272	1 ± 1
p-value	*0.460*	*0.959*	*0.504*	*0.199*	*0.314*

[†]HRCT = High Resolution Computed Tomography, m[¶]= mean, [‡]SD = Stadard Deviation, [§]MII-pH = pH-impedence

No significant relation between HRCT score and MII-pH parameters was found (Table 6.); however, a direct (not significant) correlation was noticed with RI, acid refluxes and SI/SAP (respiratory symptoms), while an inverse correlation was identified with all other MII-pH parameters.

Table 6

Correlation between HRCT† score and MII-pH§ parameters (assessed by Spearman Test).

	Rs	p-value
Score HRCT†/Acid refluxes	0.022	0.925
Score HRCT†/RI‡	0.240	0.307
Score HRCT†/TNR¶	-0.435	0.055
Score HRCT†/A TNR	-0.355	0.124
Score HRCT†/WA TNR	-0.085	0.723
Score HRCT†/Al TNR˝	-0.168	0.478
Score HRCT†/PR¥	-0.282	0.228
Score HRCT†/SI°-SAP	0.041	0.865

†HRCT = High-Resolution Computed Tomography, § MII-pH = pH-impedence, ‡RI = Reflux Index, ¶TNR = Total Number Of Impedance Refluxes, A TNR = Acid TNR, WA TNR = Weakly Acidic TNR, ˝Al TNR = Alkaline TNR, ¥PR = Proximal Refluxes, °SI = Symptom Index, SAP = Symptom Association Probability.

HRCT score > 6 was associated with a 57% Se, 69% Sp, 50% PPV and 75% NPV.

Assessing the HRCT scoring system accuracy in predicting pathological MII-pH by ROC Curve, the Area Under the Curve was 0.736 (Fig. 1.). The score with the highest sensitivity and specificity resulted < 4.5 showing a NPV of 86,5% whilst a HCRT value > 7.5 had a PPV of 75%.

4. Discussion

This is the first study characterizing GER through MII-pH and analyzing the relation between GER and a High Resolution Computed Tomography score in children with idiopathic BC.

In our population 35% of children with BC had a pathological MII-pH. Our result is consistent with previous data reported in pediatric and adult population with BC, in which the prevalence of GERD ranged from 11–32% in children and from 26–75% in adult patients [7, 14, 15]. At present, the role of GER in patients with BC is uncertain because of the limited number of studies, the small sample of patients and heterogeneity in diagnostic criteria.

We could not find a significant difference in GER parameters and pathological MII-pH comparing children with or without BC. Conversely, adult patients with BC showed a doubled prevalence of GERD compared to healthy volunteers [16]. It is noteworthy that, for ethical reasons, MII-pH could not be performed in

healthy children. Hence, our comparative group was represented by children without BC but with unexplained respiratory symptoms suspected to be GER related.

In our population, gastrointestinal symptoms such as vomit, heartburn, restrosternal and abdominal pain didn't aid in identifying pathological GER as they were reported in only 3/7 (42.85%) children with pathological MII-pH and in 7/13 (53.80%) children with normal MII-pH. Previous studies demonstrated the presence of GERD in patients with respiratory disorders regardless the presence of typical gastrointestinal symptoms [7, 17].

The effect of GER in children with BC is still unclear. In our study, children with BC and pathological MII-pH did not show a different lung disease nor a more extensive lung involvement on HRCT scoring system. In adult patients with BC, Lee et al. failed to observe a correlation between GERD and severity of lung disease [16]; conversely, Koh et al. reported a reduced lung function with higher HRCT score in case of GERD [17].

According to the literature, spirometry evaluation may miss early structural lung damage and may result completely normal in early stages of BC, while lung function imparing gradually, progressing to airway obstruction [18, 19, 20]. In our population, all spirometric parameters, but FVC, were worse in children with BC and normal MII-pH than with pathological MII-pH.

Whether our results are related to the young age of patients, with limited exposure time to GER, or to the use of a not reliable diagnostic tool is unclear.

Reflux may affect respiratory tract by (micro)aspirations into the tracheobronchial tree, chemical damage, inflammatory process or by vagally-mediated reflex [7]. We didn't find any significant relation between our imaging score and MII-pH parameters, however a positive trend between HRCT score and reflux index, total acid reflux episodes and symptom indexes association (SI/SAP) was noticed, suggesting a possible role of acid GER in BC progression. Surprisingly, TNR and proximal refluxes appeared inversely associated with HRCT disproving a predominant pathogenic effect of GER aspiration in children with BC. The best therapeutic approach for GER in patients with BC is still a matter of debate. PPI are frequently used, despite they cannot contrast non acid GER neither treat microaspiration nor vagal dysregulation [7, 21]. In refractory or long term PPI dependent patients surgical intervention is also considered [12].

Interestingly, we found HRCT as a moderate accurate imaging tool in predicting pathological MII-pH. In particular, a HRCT score ≤ 4.5 showed a NPV of 86.5%, while a value ≥ 7.5 showed the best specificity (92.3%), with a PPV of 75%. If these results are confirmed in a larger population, they could be used to better select patients to start empirical treatment with PPI or to submit to MII-pH. However, we are aware of some limitations in our study:

First, this is a pilot study and data are collected on a small sample of children who could not allow to draw general conclusions. Idiopathic BC is a rare condition in children and incidence of BC strongly increases with age. A Finnish study estimated 4.9 children with BC per million person-years at age 0–14,

and 103.8 affected patients aged ≥ 65 years [22]. However, the real prevalence of BC in children is difficult to determine due to selection of patients, lack of specific symptoms and different diagnostic criteria and investigations. Next, defining GERD in children is also challenging because of unspecific clinical presentation and uncertain gold standard test. In our population we recorded both respiratory and gastrointestinal symptoms but we could not find a significant correlation between symptoms and HRCT score. Besides, because we did not perform upper endoscopy, esophageal mucosal findings could not be correlated. We analyzed GER parameters assessed by MII-pH which is currently considered the best diagnostic investigation to quantify and characterize reflux episodes and GER-symptom association. However, reference values in children with respiratory symptoms are limited and no data exist for pediatric patients with BC. Moreover, inter-observer variability in interpreting the tracings has been reported; inaccurate symptom recording is frequent and GER-symptom association time window and indexes are debated [10]. Finally, spirometry and HRCT were not performed in children without BC and our results may be biased by patient's selection. The major strength of our study is represented by combined analysis of MII-pH and spirometry parameters plus HRCT scores in a group of children with BC, not related to cystic fibrosis or other identified disorders. We also characterized GER parameters in these patients comparing them with age-matched children with persisting respiratory symptoms. Considering the negative impact of BC on patients' quality of life, a greater knowledge in their pathogenesis represent medical, social and economic unmeet need, particularly in pediatric age, when appropriate therapy may reverse the disease. To confirm the accuracy of HRCT score and to evaluate the effect of GER treatment in children with BC and pathological GER should be considered a priority of future large well-designed pediatric study. A correct management and treatment of GERD during childhood may eventually delay BC progression and improve adult outcomes.

5. Conclusions

The role of GER in BC development and lung function is still object of discussion, but 1/3 of children with BC presented a pathological MII-pH. We could not identify any respiratory symptom or MII-pH parameter characteristic of children with respiratory symptoms and BC. HRCT scoring system showed a moderate correlation with MII-pH results and a high negative predictive value when ≤ 4.5.

List Of Abbreviations

A TNR: acid total number of bolus refluxes

Al TNR: alkaline total number of bolus refluxes

BC: Bronchiectases

GER: gastroesophageal reflux

GERD: gastroesophageal reflux disease

FEV1: forced expiratory volume in one second

FVC: forced vital capacity

HRCT: High Resolution Computed Tomography

MII-pH: impedance-pH

NPV: negative predictive values

PPV: positive predictive values

PR: proximal refluxes

RI: reflux index

SAP: symptom association probability

SI: symptom index

TNR: total number of bolus refluxes

WA TNR: weakly acidic total number of bolus refluxes

Declarations

Ethics approval and consent to participate

Research was conducted in accordance with the Declaration of Helsinki (as revised in Fortaleza, Brazil, October 2013). Design and aims of the study were fully explained to all participant parents and informed consent was obtained before performing investigations.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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None.

Authors' contributions

CM planned the study and did the statistical analysis. CM, MP, SZ, MM, LM and AF acquired data. CM, GR and MP analysed and interpreted data and drafted the manuscript. SS and GVZ gave a critical revision of the manuscript for important intellectual content. All authors have read and agreed to the submitted version of the manuscript.

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Conflict of interest

None.

References

1. Smith MP. Diagnosis and Management of Bronchiectasis. Can Med Assoc J 2017; 189: E828–E835.
2. Goyal V, Grimwood K, Marchant J, Masters IB, Chang AB. Pediatric Bronchiectasis: No Longer an Orphan Disease. Pediatr Pulmonol 2016; 51: 450–469.
3. King P. Pathogenesis of Bronchiectasis. Paediatr Respir Rev 2011; 12: 104–110.
4. Chalmers JD, Chang AB, Chotirmall SH, Dhar R, McShane PJ. Bronchiectasis. Nat Rev Dis Primers 2018; 4: 45.
5. Davis SD, Fordham LA, Brody AS, Noah TL, Retsch-Bogart GZ, Qaqish BF, et al. Computed Tomography Reflects Lower Airway Inflammation and Tracks Changes in Early Cystic Fibrosis. Am J Respir Crit Care Med 2007; 175: 943–950.
6. Pappalettera M, Aliberti S, Castellotti P, Ruvolo L, Giunta V, Blasi F. Bronchiectasis: An Update. Clin Respir J 2009; 3: 126–134.
7. McDonnell MJ, O'Toole D, Ward C, Pearson JP, Lordan JL, De Soyza A, et al. A Qualitative Synthesis of Gastro-Oesophageal Reflux in Bronchiectasis: Current Understanding and Future Risk. Respir Med 2018; 141: 132–143.
8. Pasteur MC, Bilton D, Hill AT, British Thoracic Society Bronchiectasis (non-CF) Guideline Group. British Thoracic Society Guideline for Non-CF bronchiectasis. Thorax 2010; 65 Suppl 1: i1–58.

9. Rossi P, Isoldi S, Mallardo S, Papoff P, Rossetti D, Dilillo A, et al. Combined Multichannel Intraluminal Impedance and PH Monitoring Is Helpful in Managing Children with Suspected Gastro-Oesophageal Reflux Disease. Dig Liver Dis 2018; 50: 910–915.
10. Wenzl TG, Benninga MA, Loots CM, Salvatore S, Vandenplas Y; ESPGHAN EURO-PIG Working Group. Indications, Methodology, and Interpretation of Combined Esophageal Impedance-PH Monitoring in Children: ESPGHAN EURO-PIG Standard Protocol. J Pediatr Gastroenterol Nutr 2012; 55: 230–234.
11. Lopez-Alonso M, Moya MJ, Cabo JA, Ribas J, del Carmen Macías M, Silny J, et al. Twenty-Four-Hour Esophageal Impedance-PH Monitoring in Healthy Preterm Neonates: Rate and Characteristics of Acid, Weakly Acidic, and Weakly Alkaline Gastroesophageal Reflux. Pediatrics 2006; 118: e299–e308.
12. Rosen R, Vandenplas Y, Singendonk M, Cabana M, DiLorenzo C, Gottrand F, et al. Pediatric Gastroesophageal Reflux Clinical Practice Guidelines: Joint Recommendations of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition and the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition. J Pediatr Gastroenterol Nutr 2018; 66: 516–554.
13. Eichinger M, Optazaite DE, Kopp-Schneider A, Hintze C, Biederer J, Niemann A, et al. Morphologic and Functional Scoring of Cystic Fibrosis Lung Disease Using MRI. Eur J Radiol 2012; 81: 1321–1329.
14. Banjar HH. A Review of 151 Cases of Pediatric Noncystic Fibrosis Bronchiectasis in a Tertiary Care Center. Ann Thorac Med 2007; 2: 3-8.
15. Zaid AA, Elnazir B, Greally P. A Decade Of Non-Cystic Fibrosis Bronchiectasis 1996-2006. Ir Med J 2010; 103: 77-79.
16. Lee AL, Button BM, Denehy L, Roberts SJ, Bamford TL, Ellis SJ, et al. Proximal and Distal Gastro-Oesophageal Reflux in Chronic Obstructive Pulmonary Disease and Bronchiectasis: Gastric Reflux in Chronic Lung Disease. Respirology 2014; 19: 211–217.
17. Koh WJ, Lee JH, Kwon YS, Lee KS, Suh GY, Chung MP, et al. Prevalence of Gastroesophageal Reflux Disease in Patients With Nontuberculous Mycobacterial Lung Disease. Chest 2007; 131: 1825–1830.
18. Wurzel DF, Chang AB. An Update on Pediatric Bronchiectasis. Expert Rev Respir Med 2017; 11: 517–532.
19. King PT, Holdsworth SR, Farmer M, Freezer N, Villanueva E, Holmes PW. Phenotypes of Adult Bronchiectasis: Onset of Productive Cough in Childhood and Adulthood. COPD J Chronic Obstr Pulm Dis 2009; 6: 130–136.
20. Santamaria F, Montella S, Camera L, Palumbo C, Greco L, Boner AL. Lung Structure Abnormalities, but Normal Lung Function in Pediatric Bronchiectasis. Chest 2006; 130: 480–486.
21. Undem BJ, Kollarik M. The Role of Vagal Afferent Nerves in Chronic Obstructive Pulmonary Disease. Proc Am Thorac Soc 2005; 2: 355–360.
22. Saynajakangas O, Keistinen T, Tuuponen T, Kivela SL. Evaluation of the incidence and age distribution of bronchiectasis from the finnish hospital discharge register. Cent Eur J Public Health 1998; 6:235–237

Figures

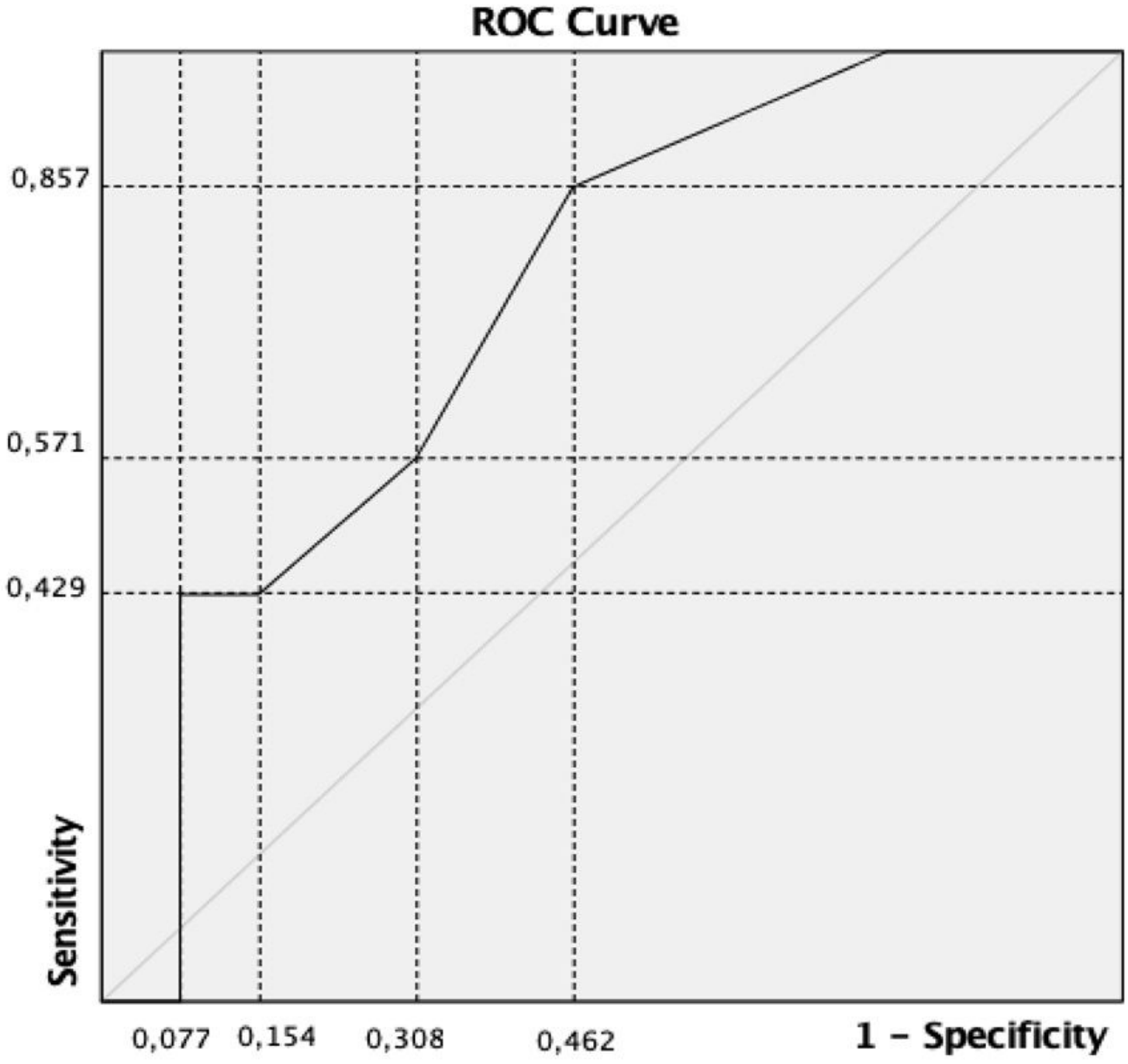

Figure 1

Analysis of the High-Resolution Computed Tomography scoring system accuracy in predicting gastro-esophageal reflux disease by ROC Curve. The Area Under the Curve was 0.736.