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Early View

Original article

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The clinical significance of oropharyngeal cultures in young children with cystic fibrosis

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Take home message:

Oropharyngeal swab cultures in children with cystic fibrosis are not helpful for ruling out lower airway *Pseudomonas* infection and are not associated with structural lung disease, lung inflammation or admissions for respiratory exacerbations.

ABSTRACT

In children with cystic fibrosis (CF) the associations between oropharyngeal swabs (OPS) for detection of *Pseudomonas* and lung disease has not been evaluated.

OPS and bronchoalveolar lavage (BAL) samples were obtained annually in children with CF from 2005 to 2017. OPS test characteristics were calculated using BAL as gold standard. Results were related to lung inflammation (BAL neutrophil elastase, interleukin-8), structural lung disease (chest CT PRAGMA-CF scores), respiratory exacerbations, and future detection of *Pseudomonas* on BAL.

From 181 patients, 690 paired OPS-BAL cultures were obtained. Prevalence of *Pseudomonas* in BAL was 7.4%. OPS sensitivity was 23.0% and specificity 91.4%, reducing the post-test probability for a positive BAL following a negative OPS to 6.3%. *Pseudomonas* on OPS was not associated with lung inflammation or respiratory exacerbations but was weakly associated with current PRAGMA-CF %disease score ($p=0.043$). *Pseudomonas* on BAL was associated with positive neutrophil elastase (OR 4.17 CI95% 2.04-8.53, $p<0.001$), increased interleukin-8 ($p<0.001$), increased all baseline PRAGMA-CF scores ($p<0.001$), progression of PRAGMA-CF scores ($p<0.05$) and increased risk of respiratory exacerbations (IRR 2.11 CI95% 1.15-3.87, $p=0.017$).

In children with CF OPS only marginally change the probability of detecting lower airway *Pseudomonas* and are not associated with lung disease indices nor exacerbations risk.

INTRODUCTION

In infants and young children with cystic fibrosis the presence of pathogenic organisms, including *Pseudomonas aeruginosa,* in the lower airways is associated with increased inflammation [1-5] and later in childhood with structural lung disease and lower lung function.[6-8] International guidelines presently recommend regular upper airway cultures in infants and young children who are too young to expectorate in order to make management decisions to treat newly acquired as well as chronic *Pseudomonas aeruginosa* infection.[9-11] For the majority of infants and young children, the collection of oropharyngeal swabs (OPS) is the main sampling technique used for bacterial surveillance purposes. The perceived value of OPS is related to previous reports of high specificity and negative predictive values[12-15] but the low sensitivity and the poor predictive accuracy of OPS to reflect lower airway infection brings the value of OPS into question[16] . Furthermore, previous studies that report the predictive value of OPS were published prior to established newborn screening and aggressive early anti-pseudomonal regimens which are likely to have reduced lower airway *P. aeruginosa* infection in young children with cystic fibrosis and, thus potentially, the predictive accuracy of OPS[4, 17, 18]. Despite recognised limitations, the standard use of OPS for bacterial surveillance and strong recommendation to treat *Pseudomonas aeruginosa* when identified in young asymptomatic children with CF have led many centres to prescribe anti-pseudomonal treatment based upon OPS culture results. Determining therapy according to OPS culture may potentially result in delayed therapy, in the case of false negative results or in administration of unnecessary treatment for false positive results. The aim of this study was to evaluate the associations between *P. aeruginosa* OPS cultures and current and future lower airway inflammation, structural lung disease, respiratory exacerbations and lower airway *P aeruginosa* infection in young children with cystic fibrosis.

METHODS

Participants

Children participating in the Australian Respiratory Early Surveillance Team for Cystic Fibrosis (AREST CF) programme at Princess Margaret Hospital in Perth, undergoing a chest computed tomography (CT) and BAL as part of annual review, were asked to participate in this study. The programme includes a bronchoscopy with BAL and a chest CT scan performed at three months of age and then annually until the age of six years as previously described.[19] All patients in this study had OPS performed at the time of the CT and BAL, thus paired upper (OPS) and lower (BAL) airway cultures were collected in each visit for each participating patient. All patient that had paired OPS and BAL performed were included in the study. Children were clinically stable at the time of assessment. Ethics approval for the research program was obtained from the hospital ethics committee. Written, informed consent was obtained from parents prior to each annual review.

Clinical practice at the hospital is to attempt eradication of *P. aeruginosa* when detected on BAL, with two weeks of intravenous antibiotics followed by four weeks of inhaled tobramycin and oral ciprofloxacin in young patients [20]. A bronchoscopy is performed after completing the eradication protocol for patients with a first lower airway *P. aeruginosa* infection and according to clinical judgment for patients with repeated *P. aeruginosa* infection. A successful eradication rate of 77% was previously shown for this protocol [20].

Positive OPS culture is not routinely treated if *P. aeruginosa* was not simultaneously detected on BAL. OPS cultures are not collected at routine clinic visits. Routine therapy for mild respiratory exacerbations, at our centre, often include inhaled or oral antibiotics targeting *P. aeruginosa*, regardless of previous BAL or OPS culture results.

Sampling procedure

Following induction of general anaesthesia, oropharyngeal swab was performed and sent for culture of *P. aeruginosa* only. Children were then intubated and a chest CT scan performed using a low dose scanning protocol with pressure-controlled inspiratory and expiratory series.[7] The endotracheal tube was replaced by a laryngeal mask airway for flexible bronchoscopy and BAL was performed first in the right middle lobe and secondly in the worst affected lobe as identified by the preceding chest CT or the lingula if the right middle lobe was the worst affected. Topical lignocaine to the vocal cords or trachea was withheld until after all microbiological samples were obtained. Suction of pulmonary secretions was delayed until the tip of the bronchoscope was below the level of the carina to avoid upper airway contamination. The first aliquot from each lobe was sent for standard microbiological processing for the existence of bacteria, fungi and viruses. For *P. aeruginosa*, the criterion for infection was the presence of the organism in any density in BAL or in any density in OPS cultures. As previously described. [21]

Inflammation

To determine inflammation levels, free neutrophil elastase activity and interleukin-8 concentration were measured, as previously described.[19, 22] The lower limit of detection of free neutrophil elastase activity was 100 $ng.mL^{-1}$ and visits were defined as neutrophil elastase positive if the concentrations were above the lower limit of detection.

Computerized tomography analysis

The PRAGMA-CF analysis method was used to determine the extent of structural lung disease. The overall extent of lung disease (%Disease) and bronchiectasis (%Bronchiectasis) was determined from inspiratory scans and the extent of trapped air (%TrappedAir) was determined

from the expiratory scan, as previously described [23]. Each computerized tomography scan used in this study was scored by only one individual. A high inter-observer and intra-observer correlation for this scoring system was previously shown [23]. The person scoring the scans was unaware of OPS or BAL results.

Hospitalisation

Information regarding hospitalization, between January 2005 and October 2017, in the 12 months following sampling was extracted from hospital records. Included for analysis were only hospitalizations for intravenous (IV) treatment of acute respiratory symptoms (respiratory exacerbations). Hospitalisations within a month of the routine bronchoscopy were excluded from analysis in order to avoid including admissions due to bronchoscopy and BAL findings alone (e.g. finding excessive thick airway secretions), which may include children who did not have respiratory symptoms reported at the time.

Statistical analysis

Data were summarized by standard descriptive statistics. Culture results for *P. aeruginosa* from the BAL samples (lower airway culture) were considered to be "gold standard" for analysis and used to determine the ability of OPS cultures (upper airway culture) to reflect current infection. Sensitivity, specificity, positive and negative predictive values and area under the receiver operating characteristic (ROC) curve were calculated using generalized estimating equations (GEE) analysis, taking into account repeated measures in the same patients. Pre and post-test probabilities were presented using Fagan's nomogram and Cohen's kappa was used for concordance analysis. Also, the ability of BAL and OPS to predict BAL culture positivity in the following annual review was assessed. Cross-sectional and longitudinal analyses were performed

comparing OPS and BAL at baseline with inflammation markers and CT outcomes in the same year and at next annual review, respectively. Mixed effects models were used for continuous outcomes and GEE models for dichotomous outcomes, clustering for repeated visits in the same patients, and correcting for age and pancreatic sufficiency. Longitudinal analyses were additionally adjusted for inflammatory or CT outcomes at baseline. Clustered negative binomial models were used to estimate incidence rate ratios for hospitalisations for respiratory exacerbations comparing children with positive and negative culture results, for both OPS and BAL. All data were analysed using Stata version 14 (College Station, TX, USA) graphs were made using GraphPad Prism 6 (La Jolla, CA, USA).

RESULTS

One hundred and eighty one patients participated in this study between March 2005 and April 2017. These patients underwent 690 annual visits in which paired upper (OPS) and lower (BAL) airway cultures were obtained. Patients' characteristics are presented in Table 1. Growth of *P. aeruginosa* was found in 10.1% (70/690) of the upper airway (OPS) cultures and in 7.4% (51/690) of the lower airway (BAL) cultures. During the study period 35 (19.3%) patients had at least one lower airway infection with *P. aeruginosa*.

Oropharyngeal Cultures as surrogates for lower airway infection

The prevalence of *P. aeruginosa* in upper and lower airway cultures, and the sensitivity, specificity, positive predictive value, negative predicted value, and area under the ROC curve for upper airway culture as a surrogate for current lower airway culture are provided in Table 2. The likelihood ratios and Fagan's nomogram demonstrates that a negative OPS culture marginally decreases the probability for a positive lower airway (BAL) culture from a pre-test probability of 7.4% to a post-test probability of 6.3%. Concordance analysis show a poor agreement between the two tests with a Cohen's kappa of 0.123. The ROC curve is provided in Figure 1.

Disease severity at time of assessment

When evaluating disease severity as assessed by inflammatory and structural lung disease present at the time of the annual visit, a positive *P. aeruginosa* culture on OPS did not have a significant association with any markers of inflammation and had borderline significant association to only one of the PRAGMA CT scores (%disease, p=0.054 before adjusting for age and pancreatic sufficiency and p=0.043 after adjustment) table 3, this association was lost after adjusting for concurrent BAL results (p=0.11). In contrast, a positive *P. aeruginosa* culture on BAL was

significantly associated with the presence of neutrophil elastase on BAL, elevated IL-8 levels on BAL and with an increase in all structural lung disease scores as measured by PRAGMA CT (%Disease, %Bronchiectasis, %TrappedAir, $p<0.001$), Table 3 and Figure 2.

Impact on future disease and future lower airway *P. aeruginosa* infection

Oropharyngeal swab results, BAL and CT data for the next year were available for four hundred and ninety eight time points in 181 patients. When evaluating future disease severity as assessed by inflammatory and structural lung disease one year later, a current positive *P. aeruginosa* culture on OPS did not have any significant association with any future markers of inflammation, PRAGMA CT scores, or change in PRAGMA CT scores, Table 4. Conversely, a current positive *P. aeruginosa* culture on BAL was significantly associated with worse future structural lung disease, as assessed on PRAGMA CT scores (%Disease and %Bronchiectasis, $p<0.05$). Furthermore, adjusting for prior year CT scores showed that in patients with *P. aeruginosa* culture on BAL there was a significant progression in structural lung disease (%Disease and %Bronchiectasis on PRAGMA CT scores, $p<0.05$) one year later, Table 4.

The prevalence of lower airway (BAL) *P. aeruginosa* one year later was 7.6% (38/498). Patients with *P. aeruginosa* culture on BAL but not on OPS had an increased risk for positive *P. aeruginosa* on BAL in the next annual review (Odds ratio 5.18, 95% confidence interval 2.22 to 12.07, $p<0.001$ Vs. Odds ratio 2.03 95% confidence interval 0.85 to 4.87, $p=0.11$, respectively). Importantly, as mentioned above, the practice in this hospital is to treat *P. aeruginosa* when detected on BAL, positive OPS cultures performed at the time of BAL are not routinely treated.

Hospitalizations for Respiratory Exacerbations

Data on hospitalization for respiratory exacerbations are presented in Table 4. Two hundred and nineteen hospital admissions were recorded in participating patients during the study period. Excluded from risk analysis were 51 admissions for eradication of *P. aeruginosa* detected on BAL, two admissions for eradication of MRSA detected on BAL, and another 27 admissions which occurred in close proximity (within a month) to the bronchoscopy. One hundred and thirty-nine admissions were included in the risk analysis.

Importantly, following the 51 admissions for eradication of *P. aeruginosa* a "post eradication regimen" bronchoscopy was performed in 30 occasions with a successful eradication documented in 28 (93%).

Patients with positive *P. aeruginosa* infection on an OPS were not at an increased risk for hospitalizations for respiratory exacerbation in the year following culture when compared to patients with a negative OPS, incidence rate ratio 1.03 ($CI_{95\%}$ 0.54-1.97, p=0.91). In contrast, the incidence rate ratio for hospitalization for subjects with positive vs. negative BAL was 2.09 ($CI_{95\%}$ 1.14-3.81, p=0.016). Since these results were obtained after exclusion of admissions for *Pseudomonas* eradications and early post bronchoscopy admissions (as described above) they might even underestimate the risk for hospital admission in lower airway *P. aeruginosa* infection.

DISCUSSION

In this large observational study of prospectively collected data in young children with cystic fibrosis, OPS cultures for *P. aeruginosa* were poorly concordant to BAL culture results and were not associated with markers of lung disease severity. Neither positive nor negative OPS cultures were correlated to lower airway inflammation or progression of structural disease, or associated with hospitalizations for respiratory exacerbations or predict future lower airway infection with *P. aeruginosa*, despite the fact that no routine treatment was directed against positive OPS in asymptomatic patients. In contrast, *P. aeruginosa* infection on BAL was associated with lower airway inflammation, current and progression of structural lung disease and with an increased risk for respiratory exacerbations and future lower airway *P. aeruginosa* infection. Our results, from a well-characterised, unselected cohort, provide objective and definitive data with which to assess the clinical utility of upper airway bacterial surveillance in young children with cystic fibrosis.

Previous studies assessing the significance of upper airway culture results in children with cystic fibrosis have shown, very similar to our results, that OPS underrepresent bacteria associated with airway inflammation when compared to lower airway cultures and that in young children with cystic fibrosis increased endobronchial inflammation is associated with *P. aeruginosa* infection on BAL and not with upper airway *P. aeruginosa* positive cultures[3, 4]. To the best of our knowledge no prior study has evaluated the relation between upper airway culture results and clinic parameters such as presence and progression of structural lung disease on chest CT scans, respiratory symptoms or risk for respiratory exacerbations. In contrast, the presence of pathogenic organisms in the lower airways, especially *Pseudomonas aeruginosa*, in children with cystic fibrosis has been repeatedly shown to be associated with worse clinical outcomes[1-8].

Current guidelines recommend the use of oropharyngeal cultures for bacterial surveillance in young children with cystic fibrosis[9, 10] despite stating that oropharyngeal cultures do not reliably predict the presence of pathogens in lower airways.[9, 24, 25] Current practice to routinely evaluate OPS and consider treatment according to culture result is largely based on the findings that OPS cultures have high specificity and negative predictive values for the detection of lower airway *P. aeruginosa* infection[12-15] Consequently, several reports have suggested that OPS cultures can be used to rule out *P. aeruginosa* infection, with a negative predictive value of over 90%.[9, 14] Importantly, negative predictive value is heavily dependent on the disease prevalence. In our cohort 7.4% of children had *P. aeruginosa* in BAL, similar to previous reports (8-11%) in young children,[12, 14] implying that the negative predictive value cannot be lower than 92.6%, regardless of the test characteristics. In order to rule out *P. aeruginosa* with certainty OPS would need to have a very high sensitivity and, consequently, very low rates of false negatives. Our study confirms previous reports that the sensitivity of OPS is relatively low. As a result of this a negative OPS result reduced the probability for a positive BAL only marginally from 7.4% (pre-test) to 6.3% (post-test). This is unlikely to be associated with any meaningful clinical consequences and explains the lack of significant associations between OPS results and the tested clinical outcomes.

The lack of correlation between OPS results and clinical outcomes and marginal effect on ruling out a lower airway *P. aeruginosa* infection brings to question the safety and efficiency of treating patients according to their OPS culture results. Using OPS results to guide treatment may result in administration of unnecessary or in delayed therapy. i.e.: In our cohort, 83% (58/70) of patients with a positive OPS would be receiving unnecessary treatment (due to a false positive result) and 76% (39/51) of patients with a lower airway *P. aeruginosa* infection will not be

receiving appropriated timely treatment (due to a false negative result). This carries both the risk of adverse drug reactions in healthy individuals as well as failing to prevent the progression of lung disease by early initiation of treatment in patients.

Indeed, routine use of OPS is a matter of ongoing debate in asymptomatic young patients and many have stressed that an alternative method should be considered for early detection of lower airway *P. aeruginosa* infection preventing progression of lung disease.[4, 12, 26] This is especially true in view of our results which show worse clinical outcomes in children with *P. aeruginosa* BAL infection demonstrating that annual surveillance with BAL is not sufficient to prevent disease progression. Although, the progression in structural lung disease seen in patients with *P. aeruginosa* BAL infection may also be related to ongoing inflammation.

Currently, alternative methods used in clinical practice include oropharyngeal suctioning after cough stimulation or after sputum induction with hypertonic saline. Both methods were recently compared to BAL: the cough stimulation technique showed high specificity and slightly better sensitivity than OPS[27] and the sputum induction technique showed variable results with good bacteriologic correlation in small study[28] but low specificity, sensitivity and predictive values in a larger study.[21] Use of molecular diagnostic techniques on routine clinical samples holds the promise of improved accuracy in the diagnosis of infection. Molecular techniques, such as polymerase chain reaction have high sensitivity for detection of *P. aeruginosa* in expectorated sputum, but no study has yet evaluated to the use of polymerase chain reaction on BAL fluid in young non-expectorating children with cystic fibrosis. Further research is warranted to investigate if molecular techniques applied to upper airway samples may provide improved accuracy in early detection of lower respiratory tract pathogens in young asymptomatic patients with cystic fibrosis.[16] A promising technique is the analysis of compounds in exhaled breath. Hydrogen cyanide in exhaled breath has been shown to be a specific marker of *P. aeruginosa*

infection in children and adults [29-31]. Gas chromatography-mass spectrometry techniques analysing volatile organic compounds in exhaled breath may, in the future, also improve the sensitivity for detection of *P. aeruginosa* and allow real time infection risk assessment, thereby facilitating appropriate clinical decision making. [32, 33]

The study has several limitations: much like previous studies comparing OPS to BAL,[12-14] samples were obtained in anaesthetised children, which has raised concerns that samples do not sufficiently reflect OPS obtained in routine clinical practice. Still, we have identified more *P. aeruginosa* in OPS than BAL cultures and predictive values of our results match with previous reported studies demonstrating that the culture technique is at least adequate. Secondly, OPS were sampled in stable individuals during a routine annual review, therefore our results may not be fully generalised to the clinical significance of OPS in symptomatic young patients with cystic fibrosis. Furthermore, OPS are not routinely collected in our centre at each visit, thus we have no data on the value of frequent repeated upper airway sampling which has been shown to reduce the number of false negative cultures.[15] Performing repeated OPS at quarterly intervals might have allowed a better evaluation of the temporal association between upper and lower airway infection. Thirdly, molecular typing of the *P. aeruginosa* strains isolated in OPS and BAL cultures were not available in current study. Molecular typing may have assisted in accurately characterizing the association between current and future upper and lower airway infections. Notably, previous studies assessing this association have shown a molecular discordancy between BAL and oropharyngeal *P. aeruginosa* strains [12, 34].

The main strength of our study lies in the large number of included patients with annually repeated paired OPS and BAL cultures and the longitudinal design. This is the largest study to-date comparing results from paired upper and lower airway cultures in young clinically stable

children with cystic fibrosis and the longitudinal design enables assessment of the clinical significance of the culture results.

In summary, OPS *Pseudomonas* culture results only slightly reduce the probability for a negative lower airway infection and are not associated with parameters of lower airway disease in young clinically stable patients with cystic fibrosis. These findings do not support the routine use of OPS cultures in ruling out lower airway infections and highlight the need to develop a more robust feasible method for early detection of lower airway *P. aeruginosa* infection which will help guide treatment and prevent or delay the progression of destructive lung disease in young children.

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Table 1. Study population characteristics at the annual reviews

Characteristic	
Study participants	n=181
Gender (Male, %)	99 (55%)
Pancreatic sufficiency, N (%)	27 (15%)
Total number annual visits (with paired OPS and BAL)	n=690
Number of visits per patient, median (range)	3.8 (1-8)
Age patient at visit in years, median (IQR)	3.02 (1.24, 4.91)
Number of visits with BAL inflammatory markers	668
Number of visits with CT scans (PRAGMA-CF)	550

BAL = bronchoalveolar lavage; CT = computed tomography; OPS = oropharyngeal swab; IQR=interquartile range; PRAGMA-CF = Perth-Rotterdam Annotated Grid Morphometric Analysis for Cystic Fibrosis

Table 2. Prevalence of organisms, diagnostic accuracy and likelihood ratios of oropharyngeal swabs compared to BAL for detection of *P. aeruginosa*.

Characteristic	**(95% CI)**
Bronchoalveolar lavage positivity, % (n)	7.4% [51/690]
Oropharyngeal swab positivity % (n)	10.1% [70/690]
Sensitivity	23.0% (13.5%, 36.4%)
Specificity	91.4% (88.3%, 93.7%)
Positive predictive value	18.2% (10.4%, 29.8%)
Negative predictive value	93.7% (90.6%, 95.8%)
Area under ROC curve,	0.57 (0.51, 0.63)
Positive likelihood ratio	2.59 (1.49, 4.5)
Negative likelihood ratio	0.84 (0.72, 0.98)
Pre-test probability	7.4%
Post-test probability in case of a:	
Positive test	18.2% (10.4%, 29.8%)
Negative test	6.3% (4.2%, 9.4%)
Cohen's Kappa	0.123

Data presented as % (95% CI) unless otherwise specified. All calculations performed using Generalized Estimating Equation (GEE) models to correct for correlated measurements in same individuals.

Table 3. Association of BAL and OPS infection status with inflammatory markers and PRAGMA CT score in the same year

Variable	**BAL culture (pos. vs neg.)**		**OPS culture (pos. vs neg.)**	
Inflammatory markers N=668	**Odds Ratio ($CI_{95\%}$)**	**P value**	**Odds Ratio ($CI_{95\%}$)**	**P value**
Neutrophil elastase	OR=4.17 (2.04-8.53)	<0.001	OR=1.17 (-0.58-2.40)	0.658
	Difference ($CI_{95\%}$)	**P value**	**Difference ($CI_{95\%}$)**	**P value**
IL8 levels (logscale)*	0.92 (0.55-1.29)	<0.001	0.26 (-0.07-0.59)	0.124
PRAGMA CT scores N=550				
% Disease	1.56 (0.96-2.16)	<0.001	0.55 (0.02-1.08)	0.043
% Bronchiectasis	0.57 (0.24-0.90)	0.001	0.08 (-0.20-0.37)	0.561
% Trapped air	4.12 (2.05-3.19)	<0.001	0.66 (-1.16-2.18)	0.479

Mixed models for continuous outcomes, Generalized Estimating Equation models used for dichotomous outcome (i.e. Neutrophil elastase yes/no). Analyses clustered for repeated measures in same patient, and adjusted for age at visit and pancreatic sufficiency. BAL = bronchoalveolar lavage; OPS = oropharyngeal swab. PRAGMA = Perth-Rotterdam Annotated Grid Morphometric Analysis.

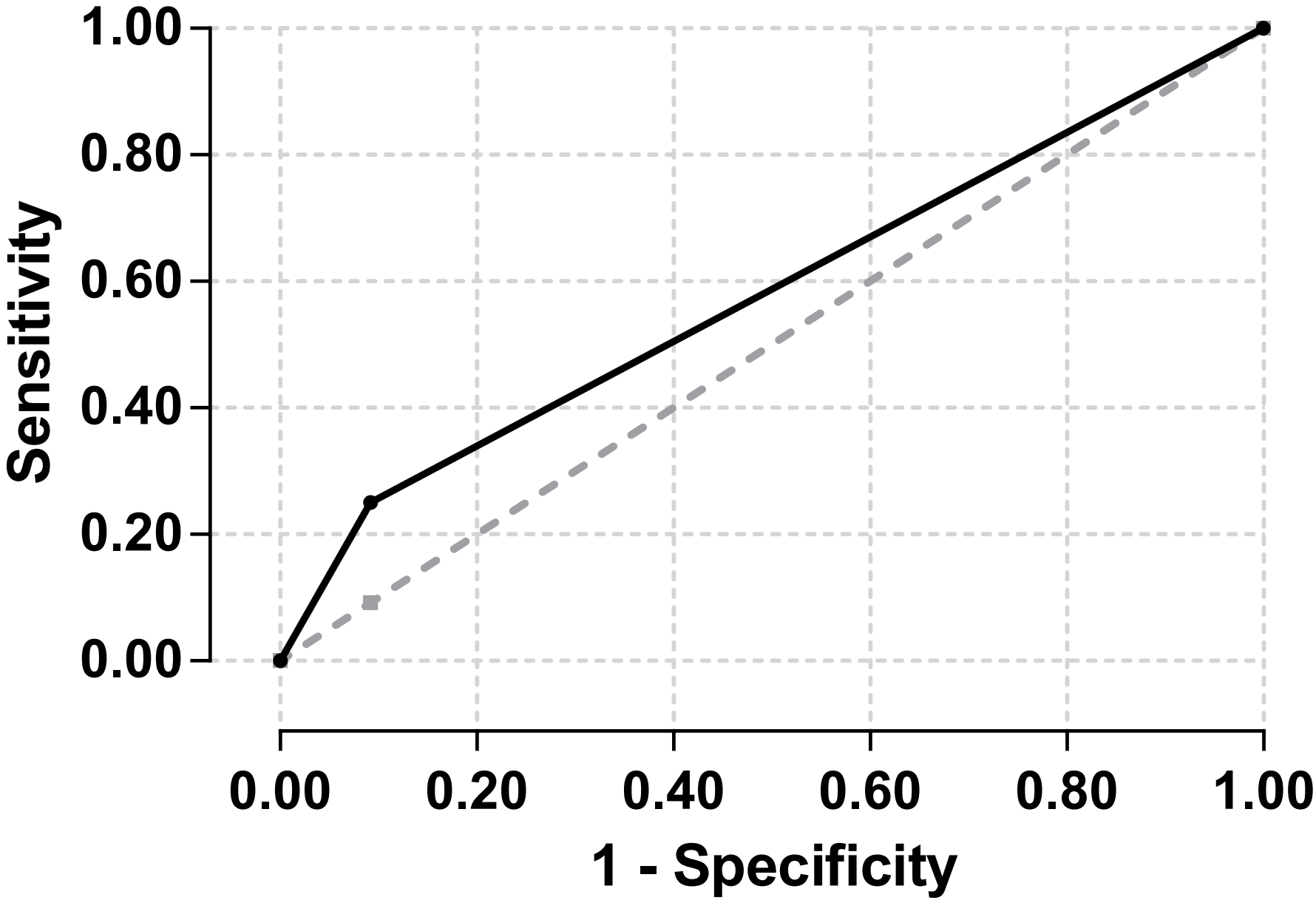
Table 4. Association of BAL and OPS infection status with inflammatory markers, PRAGMA CT score, and admission rates for respiratory exacerbations in the following year

Variable	**BAL culture (pos. vs neg.)**		**OPS culture (pos. vs neg.)**	
Inflammatory markers N=470	**Odds Ratio ($CI_{95\%}$)**	**P value**	**Odds Ratio ($CI_{95\%}$)**	**P value**
Neutrophil elastase	OR=1.26 (0.50-3.17)	0.317	OR=1.32 (0.60-2.94)	0.491
	Difference ($CI_{95\%}$)	**P value**	**Difference ($CI_{95\%}$)**	**P value**
IL8 levels	0.20 (-0.27-0.67)	0.408	0.34 (-0.04-0.726)	0.083
PRAGMA CT scores progression N=369				
% Disease	0.82 (0.07-1.58)	0.031	-0.23 (-0.85-0.40)	0.481
% Bronchiectasis	0.60 (0.23-0.97)	0.001	0.01 (-0.30-0.33)	0.933
% Trapped air	0.19 (-2.56-2.93)	0.895	-0.15 (-2.50-2.20)	0.901
Respiratory exacerbations following BAL* *N=690*	**IRR ($CI_{95\%}$)**	**P value**	**IRR ($CI_{95\%}$)**	**P value**
	2.11 (1.15, 3.87)	0.017	1.01 (0.53, 1.90)	0.983

Mixed models for continuous outcomes, Generalized Estimating Equation models used for dichotomous outcome (i.e. Neutrophil elastase), negative binomial model for count (number of admissions). All analyses clustered for repeated measures in same patient, adjusted for age at visit and pancreatic sufficiency. Analyses on inflammatory markers and CT scores in following year adjusted for respective results at time of airway sampling. *: In 12 months following BAL, excluding admissions in first month after BAL. BAL = bronchoalveolar lavage; OPS = oropharyngeal swab; IL8 = interleukin 8; IRR = Incidence rate ratio; CT = computed tomography. PRAGMA = Perth-Rotterdam Annotated Grid Morphometric Analysis.

Figure 1. Receiver operator characteristic curve (ROC) of oropharyngeal swabs to predict lower airway (bronchoalveolar lavage) infection with *P. aeruginosa.*

Figure 2. Frequency of PRAGMA CT scores according to BAL (A, B and C) and OPS (D, E and F) infection status. BAL – bronchoalveolar lavage, OPS – oropharyngeal swab.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0.80
0.60
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0.00
Sensitivity
0.00
0.20
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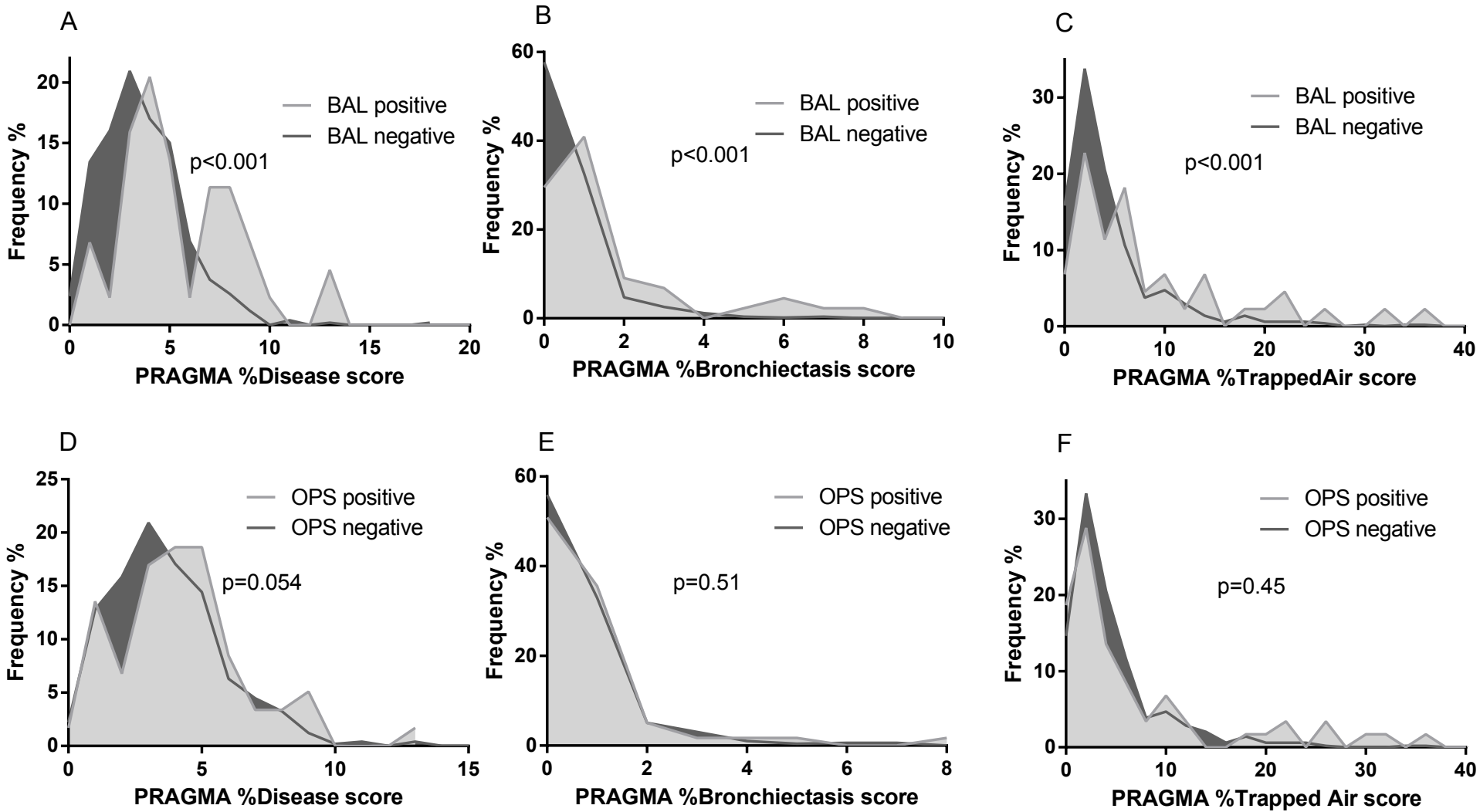
0.60
0.80
1.00
1 - Specificity


A
Frequency %
BAL positive
BAL negative
p<0.001
PRAGMA %Disease score
B
Frequency %
BAL positive
BAL negative
p<0.001
PRAGMA %Bronchiectasis score
C
Frequency %
BAL positive
BAL negative
p<0.001
PRAGMA %TrappedAir score
D
Frequency %
OPS positive
OPS negative
p=0.054
PRAGMA %Disease score
E
Frequency %
OPS positive
OPS negative
p=0.51
PRAGMA %Bronchiectasis score
F
Frequency %
OPS positive
OPS negative
p=0.45
PRAGMA %Trapped Air score