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Original Research

SIGNS AND SYMPTOMS OF CHEST DISEASES

Bronchoscopic and High-Resolution CT Scan Findings in Children With Chronic Wet Cough

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Background: **Chronic wet cough strongly suggests endobronchial infection, which, if left untreated, may progress to established bronchiectasis. Our aim was to compare the effectiveness of chest high-resolution CT (HRCT) scanning and flexible bronchoscopy (FB) in detecting airway abnormalities in children with chronic wet cough and to explore the association between radiologic and bronchoscopic/BAL findings.**

Methods: **We retrospectively evaluated a selected population of 93 children (0.6-16.4 years) with wet cough for > 6 weeks who were referred to a specialized center and deemed unlikely to have asthma. All patients were submitted to hematologic investigations, chest radiographs (CXRs), HRCT scanning, and FB/BAL. HRCT scans were scored with the Bhalla method, and bronchoscopic findings of bronchitis were grouped into five grades of severity.**

Results: **Positive HRCT scan findings were present in 70 (75.2%) patients ($P = .76$). A positive correlation was found between Bhalla score and duration of cough ($\rho = 0.23$, $P = .028$). FB/BAL was superior to HRCT scan in detecting abnormalities ($P < .001$). The Bhalla score correlated positively with type III (OR, 5.44; 95% CI, 1.92-15.40; $P = .001$) and type IV (OR, 8.91; 95% CI, 2.53-15.42; $P = .001$) bronchoscopic lesions; it also correlated positively with the percentage of neutrophils in the BAL ($\rho = 0.23$, $P = .036$).**

Conclusions: **HRCT scanning detected airway wall thickening and bronchiectasis, and the severity of the findings correlated positively with the length of clinical symptoms and the intensity of neutrophilic inflammation in the airways. However, HRCT scanning was less sensitive than FB/BAL in detecting airway abnormalities. The two modalities should be considered complementary in the evaluation of prolonged wet cough.** ***CHEST 2011; 140(2):317–323***

Abbreviations: CF = cystic fibrosis; cfu = colony-forming units; CSLD = chronic suppurative lung disease; CXR = chest radiograph; FB = flexible bronchoscopy; HRCT = high-resolution CT; LLM = lipid-laden macrophages; p25-p75 = first and third quartiles; PBB = protracted bacterial bronchitis; RML = right middle lobe

Young children rarely expectorate sputum; therefore, the term "wet" (or "moist") cough is preferred instead of "productive" cough, which is used in older children and adults. Wet cough is indicative of the presence of excessive mucus in the airways and, when chronic, it strongly suggests endobronchial infection.[1]

Bronchiectasis is a well-defined term, especially in the adult medical literature.[2,3] Its diagnosis is currently based on high-resolution CT (HRCT) scan findings, although the adult radiologic criteria may not always be suitable for children.[4,5] Furthermore, since the stage of the disease process at which the first imaging signs appear is unknown, the diagnosis can be evasive in a number of children who have symptoms consistent with bronchiectasis but no radiologic findings. The term chronic suppurative lung disease (CSLD) is used

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to describe a diagnosis with clinical symptoms similar to those of bronchiectasis but without the characteristic HRCT scan findings.[4,6] The main symptom in both conditions is the excessive prolongation of wet cough. A similar but milder condition, which is termed

protracted bacterial bronchitis (PBB), is defined as isolated long-term (>4 weeks) wet cough, which resolves with antibiotic treatment, in the absence of alternative etiology.[4,7] These three conditions—bronchiectasis, CSLD, and PBB—may not be different entities but more likely represent the wide spectrum of airway infection, which, if left untreated, may progress from PBB to CSLD and, finally, to radiologically evident bronchiectasis.[4]

Flexible bronchoscopy (FB) and HRCT scanning are the main tools for assessing airway morphology and constitute an important part of the diagnostic workup of chronic wet cough. FB surpasses HRCT scanning in examining large airways anatomy and dynamics, identifying areas of mucosal inflammation, and providing specimens for further diagnostic studies, whereas HRCT scanning provides information on small airways anatomy and lung parenchyma.[8] We undertook a retrospective study of cases of wet cough referred to a pediatric pulmonary center to explore the effectiveness of HRCT scanning and FB and BAL variables in detecting airway abnormalities in children with chronic wet cough.

Materials and Methods

Study Population and Protocol

We retrospectively evaluated all children referred for chronic wet cough to the Allergy-Pneumonology Department of Penteli Children's Hospital from May 1996 through February 2010. Chronic wet cough was defined as a moist- or wet-sounding cough that occurred almost daily for >6 weeks without improvement. Characterization of cough quality was based on parental report and was corroborated by a physician during the clinic visit. Wheeze, when present, was also confirmed by a physician. Atopy was defined as sensitization (positive skin prick test) to at least one aeroallergen.

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All children with long-term wet cough underwent a standardized extensive laboratory investigation that has been implemented in our department since May 1996.[9] The decision for bronchoscopic examination was based on the following clinical criteria: (1) recurrent pneumonia, (2) persistent (>1 month) atelectasis, (3) assessment of airway anatomy and dynamics when the wet-sounding cough also had a "brassy" quality, (4) clinical picture that was not compatible with HRCT scan findings, and (5) failure to respond to empiric antibiotic therapy and chest physiotherapy for 2 to 3 weeks. Antibiotic treatment was discontinued for a minimum of 5 days prior to performance of FB. HRCT scans were generally performed 1 week to 2 months before bronchoscopy. When asthma was suspected as a possible cause for the clinical presentation, aggressive antiasthma treatment was instituted and only patients whose wet cough persisted were considered for bronchoscopy. Moreover, we excluded seven children who had chronic wet cough as their main symptom, underwent bronchoscopy, and were finally diagnosed with cystic fibrosis (CF) (three), immunodeficiency (one), neuromuscular disorder (one), and aspiration of foreign body (two). The Ethics Committee of "Attikon" General Hospital approved the study protocol (decision number: 7/03-08-07).

FB and BAL

Elective FB was performed when the child was clinically stable, using the most suitable of the two available bronchoscopes (2.8 mm and 4.0 mm external diameter; Olympus; Tokyo, Japan), under deep sedation with video imaging of the procedure.[10] Videos were independently reviewed by three members of the study group (K. D., M. A., K. P.). Agreement was initially attained for 73 cases (78.5%). In 16 cases (17.2%), there were two different estimations, and in four cases (4.3%) there was complete disagreement. Differences were resolved after detailed review and discussion of the videos, and consensus was reached in all cases. Although the reviews were performed independently of the radiologic evaluation, the reviewers were more or less aware of the clinical presentation and the radiologic findings, since they were the attending physicians for most of the patients and information had already been shared in a few of the cases. The definition of bronchoscopic bronchitis was based on the evidence of mucosal abnormalities/inflammation (erythema, secretions, and edema), bronchomalacia, and obliterative lesions. The bronchoscopic findings were grouped into five types according to the classification proposed by Chang et al[6] as follows: type I, mucosal abnormality/inflammation only; type II, bronchomalacia; type III, obliterative-like; type IV, malacia/obliterative-like combination; and type V, no abnormality.

BAL was carried out according to recommendations from the affected bronchus or, in case of nonfocal pathology, the right middle lobe (RML). Values higher than the upper limits of the ranges quoted by Midulla et al[11] and de Blic et al[12] were considered increased. Quantitative cultures for common aerobic and anaerobic bacteria, fungi, and mycobacteria were performed. Samples were considered positive for a particular bacterial species if they rendered growth of $\geq 10^5$ colony forming units (cfu)/mL or growth of $\geq 10^4$ cfu/mL if only one pathogen was isolated.

Radiologic Evaluation

A number of children were referred to our department from regional hospitals, where an HRCT scan had already been performed; in such cases, mostly, no additional CT scans were ordered. Children who had been submitted to HRCT scan >3 months prior to bronchoscopy were not included in the study. All HRCT scans were (re)evaluated and scored by the same pediatric radiologist (E. A.), who was aware of the children's clinical symptoms but not their previous radiologic diagnoses or bronchoscopic

findings. Radiologic scores were assigned by using the method described by Bhalla et al.[13] According to this scoring system, the highest possible score (that denotes the most severe lung involvement) is 25. The same radiologist also evaluated the CXRs that were performed in all the children on the day of their initial examination by our team, unless they had a recent (within the last 2 months) film.

Statistical Analysis

All variables are described as means with SD or medians with first and third quartiles (p25-p75), according to their fitness to normal distribution. The duration of cough was treated as a continuous and as an ordinal three-level variable, as follows: < 3 months (but > 6 weeks), 3 months to 1 year, and > 1 year. For exploration of correlations and for comparisons between variables, we used Spearman ρ and Pearson r correlation coefficients and χ^2 test, respectively. Kruskal-Wallis test and nonparametric test for trend across ordered groups were used for comparisons among more than two groups of nonnormal data. Binomial and multinomial logistic regression models were used to describe associations between independent variables and binary or categorical outcomes, respectively.

Results

The medical charts of 102 children who underwent HRCT scan, underwent FB, and fulfilled the inclusion criteria were reviewed for the purpose of this study. Ninety-three patients (age range 0.6-16.4 years) had complete clinical, radiographic, and bronchoscopic data and composed the study population. The patient characteristics are shown in Table 1. Thirty-two children (34.4%) had cough for > 6 weeks but < 3 months, 20 (21.5%) for > 3 months but < 1 year, and 41 (44.1%) for > 1 year. The presence of atopy was not associated with the history of wheezing ($P = .7$).

Spirometry (with bronchodilator reversibility) was performed in 35 children (37.6%) who were > 6 years of age. The spirometry was technically acceptable in 32 patients (34.4%). Mean (SD) of FEV_1 % and FVC % predicted values were 97.4% (8.8) and 98.3% (7.8), respectively. None of the children showed bronchodilator reversibility > 10% in FEV_1 % predicted values.

There were positive findings on CXR and HRCT scan in 59 (63.4%) and 70 (75.2%) patients, respectively ($P = .76$); all subjects with a positive CXR also had positive HRCT scan findings. The occurrence of a positive CXR was positively associated with the Bhalla score but was unrelated to the duration of wet cough and a history of recurrent pneumonia (Table 2). In addition, there was no association between the findings on the CXR and the percentage of neutrophils or the occurrence of a positive BAL culture (Table 2). A statistically significant correlation was found between the Bhalla score and the duration of cough ($\rho = 0.23$, $P = .028$); the nonparametric test for trend was also significant ($P = .024$) (Fig 1). When cough duration was treated as a continuous variable, the correlation with the Bhalla score remained significant ($r = 0.21$, $P = .049$). FEV_1 % predicted was not correlated with cough duration ($r = -0.15$, $P = .39$), and there was no correlation between the Bhalla score and patient age ($P = .44$).

On bronchoscopy, 91 children (97.8%) were found to have visible bronchitis. The most frequent abnormality was type I (n = 46, 49.4%), followed by type II (n = 36, 38.7%), type III (n = 6, 6.4%), type IV (n = 3, 3.2%), and type V (n = 2, 2.2%). The location of the bronchoscopic findings generally corresponded with the location of the abnormalities, when present, on the CT scans. One of the two cases with normal FB/BAL findings revealed a small atelectasis in the RML, whereas the other had an entirely normal HRCT scan. A significant difference was found between FB and HRCT scan in detecting abnormalities ($P < .001$). The multinomial logistic regression model analysis revealed that the Bhalla score correlated positively with bronchoscopic type III (OR, 5.44; 95% CI, 1.92-15.40; $P = .001$) and type IV (OR, 8.91; 95% CI, 2.53-15.42; $P = .001$) lesions (Table 3).

The median (p25-p75) of total cell count of BAL cytology was 12×10^6 (10×10^6-17×10^6), whereas the median (p25-p75) percentages of neutrophils, macrophages, and lymphocytes were 41% (15-69), 44% (12-66), and 8% (3-25), respectively. We also found eosinophils in 26 patients and lipid-laden macrophages (LLM) in eight patients (median [p25-p75], 7% [2-10] and 63% [42-71], respectively). The patients' ages were not correlated with BAL cell percentages, and the percentage of BAL eosinophils was not correlated with either FEV_1 or FVC ($P = .36$ and $P = .31$, respectively). No association was found between the percentages of neutrophils and LLM ($P = .88$). A positive association was found between the Bhalla score and the percentage of neutrophils ($\rho = 0.23$, $P = .036$). The percentage of neutrophils was not associated with any type of bronchoscopic abnormality. Sixty-nine (74.2%) BAL cultures were positive, and 24 (25.8%) were negative. In 52 (84%) of the cultures, we detected more than one organism (cfu $\geq 10^4$). The frequency of the organisms detected in the positive cultures is shown in Table 4.

Table 1—*Patient Characteristics*

Mean age ± SD, y	5.8 ± 3.6
Boys (girls), No.	56 (37)
Atopy	23 (25.0)
History of wheezing	25 (27.1)
Positive CXR findings	59 (63.4)
Recurrent pneumonia	26 (28.0)
Bhalla score, median, p25-p75	2, 1-4

Data are presented as No. (%) unless otherwise noted. CXR = chest radiograph; p25-p75 = first and third quartiles.

Table 2—*Associations of the Findings on Plain CXR With the Clinical and Laboratory Findings*

Clinical and Laboratory Findings	CXR Findings		OR	95% CI	*P* Value
	Positive	Negative			
Wet cough duration					
6 wk to 3 mo	20 (62.5)	12 (37.5)	1.08	0.69-1.70	.75
3 mo to 12 mo	12 (60.0)	8 (40.0)			
> 12 mo	27 (65.9)	14 (34.1)			
Recurrent pneumonia, yes/no	17 (65.4)/42 (62.7)	9 (34.6)/25 (37.3)	1.12	0.43-2.90	.80
Bhalla score, median (p25-p75)	3 (1-4)	1 (0-3)	1.50	1.03-1.92	.041
BAL culture, P/N	45 (65.2)/14 (58.3)	24 (34.8)/10 (41.7)	1.25	0.42-3.72	.68
BAL neutrophils, median (p25-p75)	45 (16-72)	43 (13-67)	1.01	0.99-1.03	.95

Data are presented as No. (%) unless otherwise noted. N = negative; P = positive. See Table 1 legend for expansion of other abbreviation.

Discussion

This study of a selected childhood population referred to a specialized center for chronic wet cough, which was not deemed to be due to asthma, showed that the severity of the radiologic findings on HRCT scan correlates positively with the duration of wet cough and with the intensity of the neutrophilic inflammation in the airways. More importantly, FB with BAL proved more sensitive than HRCT scan in detecting airway pathology in these children, whereas high radiologic scores are associated with more severe bronchoscopic lesions.

In our population, cough quality was characterized as wet by the children's parents, and this was corroborated by an attending physician during the clinic visit. Thus, we feel confident that the existing evidence of good correlation between parental and physician assessment of wet cough with bronchoscopic findings,[14] in conjunction with our inclusion criteria for bronchoscopy (failure to respond to antibiotic and antiasthma therapy and physiotherapy), define our study population fairly reliably. Regarding our methodology for the bronchoscopic staging of bronchitis, we chose to use the method reported by Chang et al[6] for children investigated for wet cough. Last, the scoring of HRCT scans was performed using the Bhalla score, which is one of the most widely accepted scores for children.[13] Different scoring systems have been used by other authors[15,16]; however, since there is a strong correlation among existing scoring systems,[17] it is highly likely that that the use of another scoring system would not have altered our results.

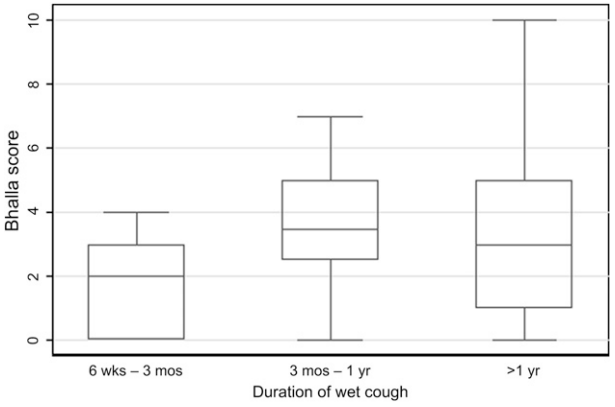

Figure 1. Bhalla score in the three groups that determine cough duration.

The relatively low Bhalla scores of our patients can be attributed to the rather mild (as compared with CF) lung impairment. With regard to the large percentage (25%) of patients who had no detectable radiographic findings on HRCT scan, this should probably be ascribed, at least in part, to the fact that in the early stages of endobronchial infection, the only radiographic sign may be bronchial wall thickening that is often difficult to assess because of its subjective nature and dependence on the window settings.[18,19] Although FB with BAL was clearly shown to be a more sensitive method to detect airway pathology in this population, HRCT scan should be considered a complementary examination, especially in light of the finding of one child who had a small RML atelectasis but normal bronchoscopic and BAL results. Indeed, bronchoscopy with BAL offers macroscopic evaluation of the larger airways and bacteriologic cultures but cannot provide data on lung parenchyma and the peripheral airways.

The large number of children (52.2%) who were referred to a specialized respiratory clinic after > 1 year duration of their symptoms is rather surprising. This may be due to the unfamiliarity of the general practitioners and pediatricians with CSLD, which is a relatively newly described entity. Indeed, it is likely that the focus of the pediatric respiratory literature on asthma in the last 2 decades has contributed to the misdiagnosis of children with chronic cough—especially when associated with wheezing—as having asthma, thus resulting in prolonged treatment only with antiasthma medication.[20,21] We postulate that the large percentage of children with wet cough and a history of wheeze (27.1%) is primarily responsible for this misdiagnosis; the lack of correlation

Table 3—*Associations Between the HRCT Scan Bhalla Score and the Bronchoscopic Classification*

Bronchoscopic Classification (Types)	Bhalla Score, Median (p25-p75)	OR	95% CI	*P* Value
I (Mucosal abnormality/inflammation)	2 (0-3)	1.65	9.77-3.44	.19
II (Bronchomalacia)	2 (1-3.5)	1.56	0.73-3.33	.24
III (Obliterative-like)	6 (5-6)	5.44	1.92-15.40	.001
IV (Malacia/obliterative-like combination)	6 (5-10)	8.91	2.53-15.42	.001
V (No abnormality)	1 (0-2)	NA	NA	NA

Classification types from Chang et al.[4] Type V (no abnormality) was treated as the reference outcome. HRCT = high-resolution CT. NA = not applicable. See Table 1 for definition of other abbreviations.

between atopy and wheeze in our study population suggests that the latter was probably due to either mucus hypersecretion producing bronchostenosis and turbulent flow or secretory hyperresponsiveness due to bacterial endotoxin.[22] We have previously reported that despite an increased frequency of airway hyperresponsiveness among children with RML syndrome, these patients are not more atopic than control subjects without asthma.[23]

Although a high frequency of positive findings was observed on plain CXR (63.4%), we failed to show an association between these findings and the various clinical and laboratory variables examined, thus suggesting that CXR findings are not prognostic of endobronchial infection. However, the usefulness of CXR as a first-line imaging modality in the investigation of children with wet cough should not be questioned, as it involves a markedly lower radiation dose to the child when compared with HRCT scan.

The duration of cough virtually denotes the duration of the disease and, not unexpectedly, was positively correlated with the Bhalla score. The correlation was low ($\rho = 0.23$), but this may be due to the rather crude classification of cough duration as a three-level ordinal variable instead of a continuous one, which has probably resulted in the loss of information, thus reducing the power of our analysis. We chose this classification because treating duration of cough as a continuous variable would have resulted in a large recall bias. In addition, despite the aforementioned limitations, when treating the duration of cough as a continuous variable, we reached similar conclusions regarding its correlation with the Bhalla score ($r = 0.21$). It is important to note that the Bhalla score has been designed to evaluate HRCT scan images of patients with CF lung disease, and, therefore, may not be as sensitive in the assessment of the more subtle morphologic changes of CSLD and PBB. An adapted scoring system should probably be devised and validated to meet the clinical and research needs of CSLD radiologic imaging.

Table 4—*Prevalence of Organisms Detected in Positive BAL Cultures and Respective Bhalla Scores*

Organism	Prevalence, % (No.)	Bhalla Scores, Median (p25-p75)
Haemophilus influenzae	34.5 (37)	3 (2-4)
Streptococcus pneumoniae	25.2 (27)	3 (1-5)
Moraxella catarrhalis	16.8 (18)	2 (0-4)
Gram-negative bacteria	11.2 (12)	3 (1-5)
Staphylococcus aureus	4.6 (5)	3 (2-3)
Pseudomonas aeruginosa	4.6 (5)	3 (1-4)
Candida albicans	1.8 (2)	3 (0-6)
Enterococcus faecalis	0.9 (1)	6 (6-6)

See Table 1 for expansion of abbreviation.

The frequency of the severity categories of our bronchoscopic findings, when grouped according to the classification proposed by Chang et al,[6] was similar to that described by the aforementioned authors ($P = .1$). However, a significant correlation of the Bhalla scores with the bronchoscopic abnormalities was detected only for the more severe types (types III and IV in Table 3) only. We found that for every unit increase in the Bhalla score, there was a more than fivefold increase in the risk of having obliterative-like lesions (as compared with having no abnormality); similarly, for every unit increase in the Bhalla score, there was an almost ninefold increase of the risk of having malacia/obliterative-like combination lesions (as compared with having no abnormality).

The BAL neutrophil differential count constitutes an important marker of endobronchial infection.[24,25] Indeed, elevated neutrophils were observed in many of our patients. We also found a positive correlation between the percentage of neutrophils and the Bhalla score. Nevertheless, there was a substantial number of patients (almost 50%), who had normal or near-normal BAL neutrophilic counts, indicating that although the neutrophilic differential count reflects the severity of involvement, it may be in the "normal" range in the more benign forms of disease. It has been proposed that inflammation in the airways could lead to the cytoplasmic accumulation of degradation products from lipid-containing membranes of inflammatory cells in alveolar macrophages (LLM). On the other hand, there is evidence suggesting that LLM are not correlated with airway inflammation.[26] In our study, only eight children were found to have LLM in the bronchi and no correlation existed

between percentages of neutrophils and LLM. We postulate that the absence of correlation was due, at least in part, to the small number of subjects with LLM in the BAL.

The concept of the progression of non-CF suppurative lung disease from PBB to CSLD and then to established bronchiectasis, which was introduced directly[4,7] or indirectly[27-30] by various groups, provides a rational pathophysiologic model for the understanding of the course of bacterial infection of the conducting airways. However, the proposed entities, especially that of PBB, cannot be clearly separated, thus demonstrating considerable overlap. The suppurative lung disease was confirmed by FB and BAL neutrophils and culture, and these investigations lend further support to the association between the radiographic and the bronchoscopically determined more severe airway disease. A second HRCT scan that would have confirmed nonreversible bronchiectasis was often deferred for ethical reasons.

The main limitation of the study is that some of the children with chronic wet cough and wheeze were considered as having asthma or responded to the antibiotics, and they were not further evaluated. Some of them might have had findings. Another limitation of our study is that the HRCT scan images were not performed by the same scanner. This is because many of the study patients were referred to our department after having been managed for relatively long periods in nonspecialized pediatric clinics, where they had been submitted to a number of laboratory investigations, including HRCT scan. To repeat HRCT scan for the sake of a more uniform and reliable evaluation of images would have been unethical; therefore, we elected not to perform repeat CT scans, except for very few selected cases.

In conclusion, chronic wet cough usually indicates neutrophilic endobronchial inflammation that often remains undiagnosed for a long period of time. The longer the duration of symptoms the more severe are the abnormalities detected on HRCT scan. FB with BAL is more sensitive than HRCT scan, but the two modalities should be considered complimentary in the diagnosis and staging of suppurative airway disease.

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Dr Alexopoulou: contributed to evaluating chest radiographs and high-resolution CT scans and contributed to and approved the final manuscript.
Dr Nicopoulou: contributed to collecting the data and contributed to and approved the final manuscript.
Dr Anthracopoulos: contributed to designing the study, evaluating flexible bronchoscopy videos, and contributed to and approved the final manuscript.
Dr Fretzayas: contributed to coordinating the study and contributed to and approved the final manuscript.
Dr Yiallouros: contributed to drafting the manuscript and contributed to and approved the final manuscript.
Dr Nicolaidou: contributed to coordinating the study and contributed to and approved the final manuscript.
Dr Priftis: contributed to designing the study, performing flexible bronchoscopies, evaluating flexible bronchoscopy videos, and contributed to and approved the final manuscript.
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