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The early examination of combined serum and imaging data under flexible fiberoptic bronchoscopy as a novel predictor for refractory *Mycoplasma pneumoniae* pneumonia diagnosis

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Abstract

The treatment role of flexible bronchoscopy (FOB) for pediatric refractory *Mycoplasma pneumoniae* pneumonia (RMPP) has been well documented. Besides, the application indication of FOB is also studied in patients with general MPP (GMPP), especially in those with large pulmonary lesions. This study was designed to examine the diagnostic value of bronchoscopic features for RMPP.

The FOB and bronchoalveolar lavage (BAL) were adopted for pediatric patients who showed clinical and radiograph indications. On the basis of the final diagnosis on discharge, patients were divided into general and refractory MPP groups. The clinical, laboratory, and bronchoscopic imaging features were retrospectively investigated between these 2 groups.

From June 2012 to May 2014, a total of 62 RMPP and 101 GMPP patients were treated with therapeutic bronchoscopy. The comparison analysis showed that the CRP, HBDH, LDH were significantly different between RMPP and GMPP groups (all $P < .001$). In the bronchoscopic imaging, the mucus plug was significantly more commonly seen in the RMPP group ($P < .001$). Receiver operating characteristic (ROC) analysis revealed that the combined serum, clinical, and FOB imaging data possessed greater specificity and sensitivity than serum and clinical data alone.

Our data suggest that the combined serum, clinical, and bronchoscopic imaging data might serve as a promising predictor for early RMPP diagnosis for pediatric patients with large pulmonary lesions.

Abbreviations: ALT = alanine transaminase, AUC = area under the curve, BALF = bronchoalveolar lavage fluid, CAP = community-acquired pneumonia, CRP = C-reactive protein, FIB = fibrinogen, FOB = flexible fiberoptic bronchoscopy, HBDH = hydroxybutyrate dehydrogenase, LDH = lactate dehydrogenase, MP = *Mycoplasma pneumoniae*, MPP = *Mycoplasma pneumoniae* pneumonia, N% = percentage of neutrophil, OR = odds ratio, PCR = polymerase chain reaction, RMPP = refractory *Mycoplasma pneumoniae* pneumonia, ROC = receiver operating characteristic, WBC = white blood cells.

Keywords: children, early diagnosis, imaging, RMPP

1. Introduction

Mycoplasma pneumoniae (MP) is a major cause of pediatric community-acquired pneumonia (CAP).[1,2] Although most of the children with MP pneumonia (MPP) can make remarkable recovery, there are still some cases showing clinical symptoms and radiological deterioration despite the administration of appropriate antibiotics for 7 days or even longer, which are defined as refractory MPP (RMPP).[3] Due to the persistent hyperpyrexia and exacerbating pulmonary lesions, RMPP may be life-threatening.[4,5]

Flexible fiberoptic bronchoscopy (FOB) has been widely applied in children with lung disease.[6,7] But even when the clinical application indication for FOB appears, physicians still find difficulties drawing a conclusion whether a child is with general or RMPP. As early intervention is important in outcome improving, the diagnostic marker of RMPP should be investigated. Currently, the reported marker is mainly based on the clinical symptoms and laboratory examinations.[8–11] Descriptive clinical information and the inconsistent reported serum characters[12] can lead to the delayed or missed diagnosis.[13] Therefore, a more intuitive monitoring approach such as FOB is thus in great need to enable effective early diagnosis of RMPP.[14–16]

In view of several reports showing FOB imaging changes in RMPP,[17–19] we hypothesized that although radiograph-proved large pulmonary lesions appear in both general and RMPP

groups, the FOB imaging features might differ in these 2 groups in the early disease process, which might be used for early RMPP diagnosis. This study was therefore conducted to investigate the potential of combined examination data for RMPP diagnosis.

2. Materials and methods

2.1. Patients and definitions

This study was conducted under a protocol reviewed and approved by the review board of Children's Hospital of Hebei Province. All the participants' guardians gave their written informed consent for participation in the study.

We retrospectively reviewed the clinical records of 62 RMPP and 101 GMPP pediatric patients treated with FOB in Children's Hospital of Hebei Province from June 2012 to May 2014. All patients included in this study were confirmed to have large pulmonary lesions by radiological examinations. Large lesion was defined as that the extent of infiltration on chest radiography was more than one-third area of the lung.[20] MPP was confirmed when there was an infiltrate on chest radiograph in combination with fever, cough, or abnormal lung auscultation[21] and MP DNA was positively detected in bronchoalveolar lavage fluid (BALF) by real-time polymerase chain reaction (PCR),[22,23] and the specific MP antibody in sera was positively detected by a micro-particle agglutination test.[24] The RMPP diagnosis was relied on the presence of persistent fever (>38.0°C) and radiological deterioration after therapy with a macrolide combined with oral prednisolone (azithromycin 10 mg/kg/day and prednisolone 1–2 mg/kg/day) for 7 days or longer.[17,25] Other MPP children were defined as having GMPP.

Patients who received corticosteroids before admission or had any underlying diseases such as tuberculosis, asthma, recurrent respiratory tract infection, congenital cardiac or pulmonary disease, rheumatic diseases, or immunodeficiency were excluded. Patients who had computed tomographic (CT) scans and X-ray of the chest >24 hours or the bronchoscopy >7 days of admission were also excluded.

2.2. Data collection

The demographics, clinical information, laboratory data, radiological, CT-scanning, and bronchoscopy findings were collected from inpatient electronic medical records and retrospectively analyzed.

The sputum or blood specimens were tested for bacterial culture and the MP infection using serology and the BALF real-time PCR assay. The serum samples were taken at the presentation of pneumonia and at least 7 days after the first collection of serum. The Mp-specific antibody was determined using a micro-particle agglutination test (the Serodia-MycoII Kit; Fujirebio, Tokyo, Japan) according to the manufacturer's instructions.[24]

Peripheral blood samples were obtained on admission for the determination of the alanine transaminase (ALT), hydroxybutyrate dehydrogenase (HBDH), white blood cells (WBC), percentage of neutrophil (N%), fibrinogen (FIB), C-reactive protein (CRP), and lactate dehydrogenase (LDH).

In addition, the following data were also recorded: the highest temperature before admission; symptoms including cough, wheeze, tachypnea, and retraction sign of 3 fossae; course of disease and febrile days before admission. Body temperature and respiratory tract signs and symptoms of subjects were examined at the beginning of study and every 8 hours thereafter. A febrile

day was defined as the body temperature exceeded 38.0°C at least once.[26]

The procedure of BALF collection has been described elsewhere.[27] The bronchoscopy imaging and the MP detection in BALF were done 2 to 7 days postadmission; all other variables were routinely collected within 24 hours of admission.

2.3. FOB imaging

According to the FOB imaging results, patients were divided into 2 groups, the blocked group: the bronchial secretion was sticky, which formed mucus plugs as flocculent, striped, or nodular shape. The mucus plug was able to be removed only by vacuum suction, the forceps, or brush; and the unblocked group: the thin secretions could be observed under FOB, and the bronchus was able to be cleared by lavage.

2.4. Statistical analysis

The χ^2 or Fisher exact test was used for categorical variables and Student t test or the Kruskal–Wallis for continuous variables. Univariate analysis was performed to identify differences between RMPP and GMPP patients. Logistic regression analysis was performed to select the variables associated with RMPP. The receiver operating characteristic (ROC) curves were drawn and the area under the curve (AUC) was measured to evaluate the potential markers of RMMP. The SPSS 16.0 software (SPSS Inc., Chicago) was used for statistical analysis. $P < .05$ was considered statistically significant.

3. Results

3.1. General information of patients

A total of 163 patients who were diagnosed with MPP and received the therapeutic FOB from June 2012 to May 2014 were enrolled in the study. In all patients, serum MP-specific antibodies were positive as shown by the serological test and/or MP DNA was positively detected by PCR, and they did not fulfill the exclusive criteria. The median age was 5.5 (0.8~12.0) years with a female-to-male ratio of 0.75. According to the diagnostic criteria of RMPP,[4,17] patients were divided into GMPP and RMPP groups (Table 1). A total of 62 patients were in the GMPP group (25 males, 37 females), with the median age of 5.6 (1.5~10.0) years. Other 101 patients were in the RMPP group (68 males, 33 females), with the median age of 5.5 (0.8~12.0) years. The gender distribution showed that the female-to-male ratio in RMPP group was significantly greater than that in the GMPP group (2.1 vs 0.7, $P < .01$), but no significant difference was found on age between RMPP and GMPP groups ($P > .05$).

3.2. Laboratory, clinical, and FOB characteristics of GMPP and RMPP patients

The median levels of N%, CRP, LDH, HBDH, FIB, and the DNA load of MP in BALF were significantly higher in RMPP children ($P < .05$, $P < .001$, $P < .001$, $P < .001$, $P < .001$, and $P < .01$, respectively) (Table 1) than those in GMPP patients.

Regarding clinical symptoms, fever was more common in the RMPP group than the GMPP group (98.0% vs 87.1%, $P = .013$). Before admission, the fever duration and the observed median peak body temperature were significantly different between RMPP and GMPP patients (7.0 vs 6.5 days, $P = .001$; 39.8 vs 39.2°C, $P < .001$). After hospitalization, the RMPP patients were

Table 1

The clinical, laboratory, and FOB features between GMPP and RMPP groups.

	Variables	GMPP (n=62)	RMPP (n=101)	P
General information	Age, y	5.6 (1.5~10.0)	5.5 (0.8~12.0)	.737
	Sex (male/female)	2.1	0.7	.001
Clinical features	Fever	54 (87.1%)	99 (98.0%)	.013
	Cough	61 (98.4)	100 (99.0)	1.000
	Tachypnea	2 (3.2)	4 (4.0)	1.000
	Wheezing	5 (8.1)	9 (8.9)	.851
	Retraction sign of 3 fossae	3 (4.8)	9 (8.9)	.511
	Febrile days before admission	6.5 (0~60)	7 (0~20)	.001
	Febrile days in hospital	1.5 (0.0~7.0)	4 (0~26)	<.001
	Peak body temperature in hospital, ℃	39.2 (36.0~40.7)	39.8 (36.0~40.5)	<.001
	Mean hospital day	12.5 (4~29)	18 (7~44)	<.001
Laboratory values	White blood cell, $\times 10^9$/L	10.4 (4.6~22.8)	11.1 (3.7~37.3)	.070
	Neutrophil (%)	59.4 (15.4~78.8)	68.4 (20.5~90.9)	.022
	C-reactive protein, CRP, mg/L	3.1 (0.1~151.0)	54.9 (0.1~290.2)	<.001
	Lactate dehydrogenase, LDH, U/L	235 (144~735)	343 (184~819)	<.001
	Hydroxybutyrate dehydrogenase, HBDH, U/L	203 (137~568)	281 (157~619)	<.001
	Alanine transaminase, ALT, U/L	14 (6~110)	19 (7~193)	.128
	Fibrinogen, FIB, g/L	3.67 (2.05~5.70)	4.87 (2.42~6.22)	<.001
	MP-antibody titer	960 (0~1280)	1280 (0~1280)	.177
FOB imaging	Mucus plug	9 (14.5%)	42 (41.6%)	<.001

Data are presented as number (percentage), median (min~max).

ALT = alanine transaminase, CRP = C-reactive protein, FIB = fibrinogen, FOB = flexible fiberoptic bronchoscopy, HBDH = hydroxybutyrate dehydrogenase, RMPP = refractory *Mycoplasma pneumoniae* pneumonia.

observed to have significantly longer febrile days (4.0 vs 1.5 days, $P < .001$) and the median hospital stay (18.0 vs 12.5, $P < .001$) (Table 1). Besides, although the large pulmonary lesions could be observed in both RMPP and GMPP patients under CT scanning (Fig. 1), the mucus plugs were more frequently found in RMPP patients (41.6 vs 14.5%, $P < .001$) (Table 1).

3.3. Multiple logistic regression analysis for RMPP markers

The nonconditional multiple logistic regression analysis of 163 cases was performed to assess markers for the differentiation of RMPP and GMPP. The sex (female) was the protection factor,
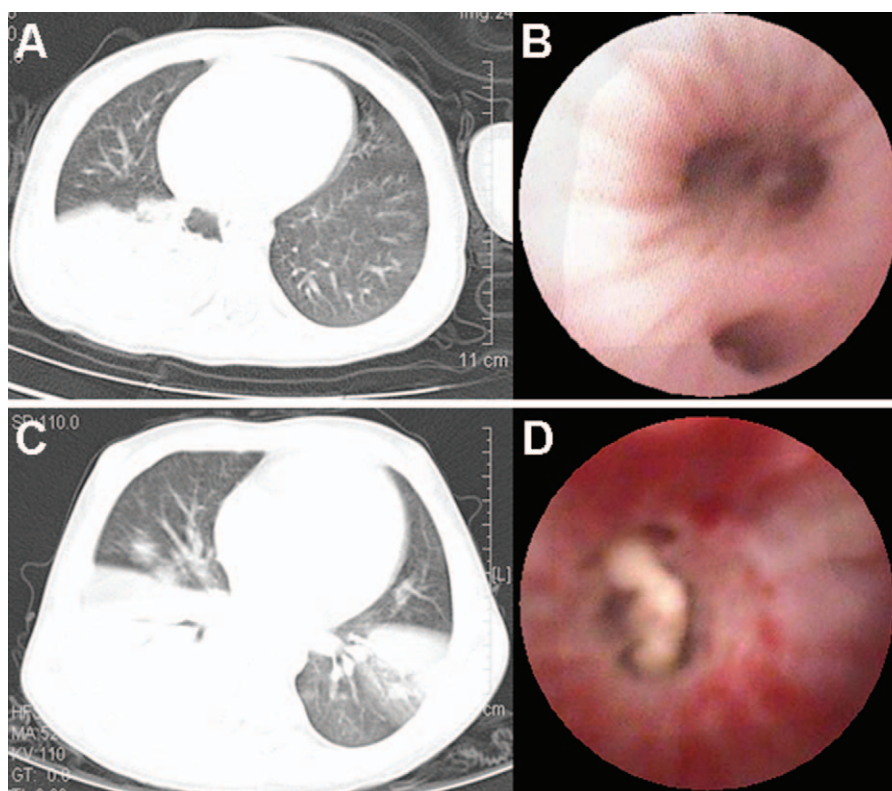

Figure 1. Imaging features. A GMPP patient under CT scanning of the chest (A) and imaging under FOB (B). A RMPP patient under CT (C) and FOB (D).

Table 2

Stepwise logistic regression analysis for the related factors predicting the RMPP.

Positive variables	B	S.E.	Wald	P	OR	95% CI Lower	Upper
Sex	−1.523	0.420	13.155	<.001	0.218	0.096	0.497
HBDH	0.006	0.002	5.729	.017	1.006	1.001	1.010
CRP	0.015	0.005	8.713	.003	1.015	1.005	1.025
Febrile day before admission	0.090	0.036	6.088	.014	1.094	1.019	1.175
Mucus plug	1.205	0.485	6.173	.013	3.337	1.290	8.634

CI = confidence interval, CRP = C-reactive protein, HBDH = hydroxybutyrate dehydrogenase, OR = odds ratio.

and HBDH, CRP, febrile days before admission, and the formation of mucus plugs possessed significantly greater predictive values as risk factors for RMPP with the odds ratio (OR) values of 0.218, 1.006, 1.015, 1.094, and 3.337, respectively (Table 2).

3.4. Predictive values of the independent correlation factors in patients with RMPP

ROC analysis showed an AUC of 0.822 for Sex-HBDH-CRP-Febrile days [$P < .001$, 95% confidence interval (95% CI): 0.755–0.889] and an AUC of 0.836 for the combination of mucus plugs with Sex-HBDH-CRP-Febrile days ($P < .001$, 95% CI: 0.771–0.900) (Fig. 2). Youden index (sensitivity+specificity-1) was further calculated to determine the optimal cut-off value of the combined predictor. The result demonstrated that the maximum Youden index was 0.564 when the cut-off value was achieved at sensitivity of 75.8% and specificity of 80.6%.

4. Discussion

MP is a common causative pathogen of respiratory infections in children.[28] Characterized by the absence of a peptidoglycan cell wall, MP infection can be effectively treated by macrolide antibiotics.[29,30] However, accumulating evidence also indicates that despite the appropriate use of macrolide antibiotics and/or corticosteroids therapy, there are still chances for aggravation of MP infection, which can progress to severe life-threatening pneumonia.[31,32] More worryingly, the prevalence of RMPP is increasing due to the abuse of macrolides and the emerging of antibiotic-resistant strains.[33,34] Therefore, the importance of markers for RMPP diagnosis has been increasingly appreciated.
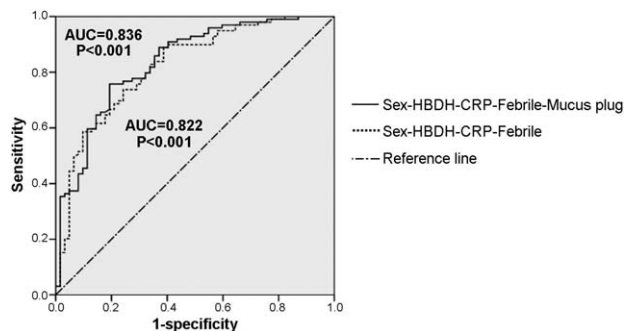

Figure 2. ROC curve analysis. ROC analysis showed an AUC of 0.822 for Sex-HBDH-CRP-Febrile days and an AUC of 0.836 for the combination of Mucus plugs with Sex-HBDH-CRP-Febrile days, suggesting that the combined predictor has a greater diagnostic value than serum and clinical data alone.

So far, various clinical and laboratory data have been employed as the predictors of RMPP,[12,13,35,36] but the more visualized characters from radiology, CT scan, and FOB have hardly been studied as potential markers for RMPP. The chest radiology and CT scan can be extremely useful in documenting regional density distribution as well as the damage level and shape in the lung.[15] The radiograph or CT scan proved-large pulmonary lesions can be observed in both general and RMPP groups. FOB, a multi-disciplinary approach, has been used not only for differential diagnosis but also in treatment.[37] It has 3 advantages: the directly visualized endobronchial observation; easy access to the lower airway for the pathogenic detection or biopsy with minimal damage; and additional therapeutic interventions once combined with bronchoalveolar lavage (BAL), such as the removal of the mucous plug.[7,9,18] Therefore, in this study, the imaging changes of FOB combined with the clinical and serum features were explored as early diagnosis markers for RMPP. The following findings were made: at the admission, the N%, CRP, LDH, HBDH, and FIB differed significantly between RMPP and GMPP patients; the formation of mucus plugs was more commonly seen in RMPP patients under FOB; and for RMPP diagnosis, the combination of gender, HBDH, CRP, febrile days before admission, and mucus plugs were shown to possess greater predictive values than serum and clinical data alone.

Actually, the altered pulmonary imaging, for example, the large lobar consolidation with high density,[38] necrosis, and pleural effusion,[39] has been observed in previous studies and more commonly seen in RMPP patients. However, many published RMPP prediction studies have not specified or recorded the imaging changes at the early admission, but during the deterioration process. It is known that a variety of factors, for example, recording time, course of disease, degree of symptoms, previous medications, etc., affect the measurement of predictors. Meticulous attention was paid to eliminate the compounding factors in the present study. First, the disease process before admission was < 10 days, and the laboratory data were recorded during 24 hours of admission. Second, the X-ray and CT scan were recorded in the 24 hours of admission. Third, patients who received corticosteroids before admission were excluded to eliminate the drug effects on the predictors. We found that, in addition to HBDH and CRP, the existence of mucus plugs possess predictive values to RMPP diagnosis.

Despite that the altered FOB imaging in patients with RMPP was demonstrated by a considerable number of studies, its sensitivity and specificity in RMPP diagnosis was seldom examined. We showed an AUC of 0.836 for RMPP diagnosis when the FOB imaging result (the formation of mucus plugs) was combined with serum and clinical data. Zhang et al[7] revealed that, compared with late BAL therapy, BAL therapy during the

early disease process in RMPP patients with large pulmonary lesions resulted in faster recovery of clinical and inflammation characters and shorter hospital stay. Corticosteroids have been used with satisfactory therapeutic effect for children with RMPP.[17] However, due to the potential risk of side effects and blurring diagnosis caused by early use of corticosteroids,[40] it is advised that physician be prudent in adopting corticosteroids. To our knowledge, this is the first study that explored the imaging changes with other characters as a combined potential predictor for RMPP diagnosis. The use of a risk score for identification of mucus plugs in RMPP patients combined with clinical and laboratory variables could identify patients who might benefit from adjunctive anti-inflammatory and BAL therapies. Further multicenter studies in larger cohorts are needed to validate these results.

In conclusion, we retrospectively analyzed the hospitalized MPP patients who had radiograph-proved large pulmonary lesions and received therapeutic FOB, and compared clinical features, laboratory data, and imaging findings under FOB between RMPP and GMPP children. We discovered for the first time that FOB imaging findings combined with clinical features and laboratory data could improve the early identification of RMPP, facilitating early and effective intervention, and preventing the further deterioration of the disease. FOB is an invasive procedure and may not be ethically appropriate in all cases as a predictor but may have therapeutic value. We included only those who had FOB as a therapeutic treatment for analysis, which is a limitation of this study.

Acknowledgment

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