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Diagnostic Value of Galactomannan in Bronchoalveolar Lavage Fluid for Chronic Respiratory Disease with Pulmonary Aspergillosis

Guangbin Lai,[a]* Chao Zeng,[a] Jianming Mo,[a] Wei-dong Song,[a] Ping Xu[a]

[a]Department of Respiratory and Critical Care Medicine, Peking University Shenzhen Hospital, Shenzhen, Guangdong, China

Guangbin Lai, Chao Zeng, and Jianming Mo contributed equally to this work. Author order was determined on the basis of seniority.

ABSTRACT The objective of this study was to explore the diagnostic value of the bronchoalveolar lavage fluid galactomannan (BALF GM) test for chronic respiratory disease with pulmonary aspergillosis and to establish the optimal cutoff value. Samples from a total of 309 chronic respiratory disease patients seen at the respiratory medicine department of Peking University Shenzhen Hospital from September 2016 to September 2019 were analyzed. According to the diagnostic criteria, we divided the patients into a case group ($n = 79$, comprising 25 proven cases and 54 probable cases) and a control group ($n = 230$). Bronchoalveolar lavage fluid was collected, and the BALF GM test results were analyzed. A nonparametric rank sum test showed that the mean rank of the case group was 255.30, which was higher than that of the control group (120.55). The Z-value was -11.567 ($P = 0.000$), indicating that the general distributions of BALF GM differed between the two groups. A BALF GM cutoff value of 0.88 showed the highest diagnostic efficacy for pulmonary aspergillosis. The sensitivity, specificity, positive predictive value, and negative predictive value were 77.2%, 93%, 79.2%, and 92.2%, respectively. As the cutoff value increased, the specificity and sensitivity of the BALF GM test increased and decreased, respectively. The BALF GM test can be used confirm the diagnosis of patients with pulmonary aspergillosis and chronic respiratory disease. The optimum BALF GM cutoff value is 0.88.

KEYWORDS aspergillosis, bronchoalveolar, lung infection

According to the World Health Organization (WHO) definition (1), chronic respiratory disease refers to a group of chronic diseases that affect the airways and other structures of the lungs. The most important of these are chronic obstructive pulmonary disease (COPD), bronchial asthma, and bronchiectasis. Chronic respiratory disease with pulmonary aspergillosis (PA) is occult and has a high mortality rate. In the retrospective study by Guinea et al. (2), *Aspergillus* was isolated from 239 of 14,618 patients with COPD; pulmonary aspergillosis was diagnosed in 53 patients, 38 of whom died within 4 months of diagnosis (mortality rate, 71.6%). The situation is particularly severe in South China with a humid and warm subtropical climate. Early diagnosis of this type of disease is particularly important, and the bronchoalveolar lavage fluid galactomannan (BALF GM) test is a useful auxiliary diagnostic modality. Indeed, in 2016, Infectious Diseases Society of America (IDSA) recommended BALF GM as a diagnostic marker for invasive aspergillosis; they consider a cutoff value of 0.5 or greater to be positive for serum or BALF (3). However, there is no consensus on a GM reference value in alveolar lavage fluid in patients with chronic airway disease but without immunodeficiency. We collected BALF from patients with chronic respiratory disease and evaluated the utility

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Address correspondence to Wei-dong Song, Songwd123@hotmail.com, or Ping Xu, ping-xu@hotmail.com.

* Present address: Guangbin Lai, Department of Respirology, Maoming People's Hospital, Maoming, Guangdong, China.

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TABLE 1 The composition ratio of chronic respiratory diseases in the two groups

Chronic respiratory disease	No. (%)		Total no.
	Case group (pulmonary aspergillosis)	Control group (nonpulmonary aspergillosis)	
COPD	23 (29.10)	81 (26.20)	104
Bronchial asthma	29 (36.70)	72 (23.30)	101
Bronchiectasis	27 (34.10)	77 (24.90)	104
Total	79	230	309

of the BALF GM level as a diagnostic marker of, and treatment target for, chronic respiratory diseases with pulmonary aspergillosis.

MATERIALS AND METHODS

Enrollment. A total of 309 patients admitted to the hospital from September 2016 to September 2019 due to chronic respiratory diseases (COPD, bronchial asthma, or bronchiectasis) were enrolled based on the following criteria: (i) risk of pulmonary infection (imaging examination revealed the presence of lung lesions); (ii) no contraindications for bronchoscopy and provision of informed consent; (iii) no allergic bronchopulmonary aspergillosis or positive *Aspergillus fumigatus* skin test; (iv) no antifungal drugs were used within 3 months prior to admission. The study protocol was approved by the ethics committee of Peking University Shenzhen Hospital. All participants of the study consented to the publication of the data.

Diagnostic classification and group assignment. Diagnostic criteria refer to the 2016 IDSA guidelines on *Aspergillus* infection diagnosis and treatment (4), together with the diagnostic criteria for invasive fungal infections used in China (5). The cases of chronic respiratory disease with pulmonary aspergillosis were classified as follows: (i) proven (confirmed diagnosis) according to a lower respiratory tract specimen positive for *Aspergillus*, with confirmation by molecular, immunological, and/or culture methods that the observed hyphae were of *Aspergillus*; (ii) probable (clinical diagnosis) according to frequent use of hormones or repeated use of broad-spectrum antibiotics for 3 months, suggestive pulmonary imaging changes within 3 months, and positive for *Aspergillus* or a positive result of a blood or BALF GM test; (iii) nonpulmonary aspergillosis if the symptoms/signs do not meet the clinical manifestations or imaging features of pulmonary aspergillosis and microbiological or pathological diagnosis does not match. According to the above-described diagnostic criteria, the cases were divided into two groups: (i) case group (pulmonary aspergillosis), including those with confirmed or clinical diagnosis of pulmonary aspergillosis, from which GM in BALF was measured before antifungal therapy; (ii) control group (nonpulmonary aspergillosis), including patients with chronic obstructive pulmonary, asthma, and bronchiectasis in which there was no evidence of *Aspergillus* infection after relevant examinations (microbiological or pathological examination). All patients enrolled were analyzed for general clinical data, pathogen examination, imaging examination, and GM detection in BALF.

Patient-specific data. A total of 309 patients with chronic respiratory disease were enrolled (182 men and 127 women), comprising 104 patients with chronic obstructive pulmonary disease, 101 with bronchial asthma, and 104 with bronchiectasis. According to the above-described diagnostic criteria, the groups were as follows. (i) The case group ($n = 79$) comprised 40 male patients, aged between 25 and 73 years with a median age of 55 years, and 39 female patients, aged between 23 and 77 years with a median age of 59 years; 25 patients had pulmonary aspergillosis confirmed by fiberoptic bronchoscopy or lung biopsy and 54 patients had clinically confirmed pulmonary aspergillosis by BALF or sputum culture suggesting *Aspergillus* infection. (ii) The control group ($n = 230$) comprised 142 male patients, aged between 24 and 78 years with a median age of 51 years, and 88 female patients, aged between 22 and 69 years with a median age of 49 years. The respiratory disease distributions of the two groups of patients can be seen in Table 1. There was no significant difference in basic characteristics between the case and control groups ($P > 0.05$) (Table 2).

Collection and processing of BALF. According to the results of chest computed tomography (CT), bronchoscopy and bronchoalveolar lavage were performed without antifungal therapy. Bronchoalveolar lavage examinations were performed according to the expert consensus (6). According to lesion severity, the right middle or left upper lobe was selected in patients with diffuse lesions in both lungs (5, 7). The diseased lung segment or subbronchial tube was inserted through a fiberoptic bronchoscope, and 60 to 80 ml of sterile physiological saline was directly injected for lavage. Five milliliters of the mixed recovered BALF was used for GM detection followed by routine BALF cell sorting and microbiological examination.

Main instruments and reagents. This study included the use of the Platelia *Aspergillus* enzyme-linked immunosorbent assay (ELISA) kit (GBD, USA) and a Bio-Rad 680 microporous microplate reader (Bio-Rad, USA). The reagents and instruments were used in accordance with the manufacturers' instructions.

BALF GM assay. GM in BALF was quantified by sandwich assay using an antibody against *Aspergillus* GM. The absorbance value was determined in accordance with the instructions of the enzyme-linked immunosorbent assay kit for *Aspergillus*, and the galactomannan index (GMI) value was calculated. Negative and positive controls were performed in each experiment (GMI = patient A value/standard A value).

TABLE 2 Comparison of the general conditions of the two groups of patients

Characteristic	Value[a]		Statistic[b]	*P* value
	Case group	Control group		
No. of cases	79	230		
Male sex	40 (50.6)	142 (61.7)	2.996	0.083
Age (yr)	59.06 ± 16.06	53.604 ± 16.09	−2.603	0.552
Hospital stay (days)	9.43 ± 3.90	8.88 ± 3.10	−1.275	0.087
White blood cell count ($\times 10^{12}$/liter)	7.03 ± 2.64	6.70 ± 2.33	−1.044	0.481
No. of platelets ($\times 10^{9}$/liter)	259.70 ± 77.71	254.95 ± 72.96	−0.491	0.313
Hemoglobin (g/liter)	129.0 ± 15.95	132.23 ± 14.52	1.663	0.087
Total protein (g/liter)	68.22 ± 7.64	71.43 ± 7.37	3.314	0.572
Albumin (g/liter)	38.72 ± 6.83	43.30 ± 6.40	5.383	0.981

[a]Values are presented as *n* (%) or mean ± standard error.
[b]The count data are represented by the χ^2 value; the measurement data are represented by the *t* value.

Data analysis. Data were analyzed using SPSS software (ver. 23.0; SPSS Inc., Chicago, IL, USA). Measurement data are presented as means ± standard deviations, and count data are presented as percentages or numbers of cases. The data were tested for normality; normally distributed data were evaluated by independent sample *t* test and chi-square test, and non-normally distributed data were subjected to nonparametric tests. The diagnostic efficacy of BALF GM was evaluated by calculating the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV). Finally, a receiver operating characteristic (ROC) curve was constructed to determine the optimum cutoff value of BALF GM.

RESULTS

BALF GM. By a nonparametric rank sum test, the mean rank of the case group was 255.30, which was higher than that of the control group (120.55). The BALF GM value of the case group was higher than that of the control group. Mann-Whitney U and Wilcoxon W tests yielded a Z-value of −11.567 ($P = 0.000$); the general distribution of BALF GM in the two groups was different (Table 3).

Diagnostic efficacy of the BALF GM test. We constructed a ROC curve (Fig. 1) and evaluated the diagnostic efficacy of BALF GM for chronic respiratory disease with pulmonary aspergillosis by calculating the Youden index and the area under the curve (AUC) (Tables 4 and 5). The diagnostic efficacy was highest with a BALF GM cutoff value of 0.88, for which the sensitivity, specificity, PPV, and NPV were 77.2%, 93%, 79.2%, and 92.2%, respectively. Sensitivity decreased, and specificity increased, as the BALF GM cutoff value increased.

DISCUSSION

The incidence of pulmonary aspergillosis in patients with chronic respiratory diseases is increasing (7). Because of its atypical clinical manifestations, pulmonary aspergillosis can be obscured by the symptoms of chronic respiratory diseases. Without treatment, the mortality rate increases significantly (8), and patients with acute exacerbations of chronic respiratory diseases suffer cough and shortness of breath. Such patients may also have concomitant aspergillosis, which can be detected by chest imaging and is characterized by multiple plaques; when it cooccurs with invasive pulmonary aspergillosis (IPA), the symptoms are likely to be confusing. Therefore, it is important to improve the diagnostic accuracy for chronic respiratory diseases cooccurring with IPA (9). Pathogen culture takes some time to perform and has a low positive rate and so is of limited utility for early diagnosis of pulmonary aspergillosis. Furthermore, the decision for histopathological examination must be based on the patient's tolerance and economic resources, limiting its clinical utility. GM in serum, BALF, or cerebrospinal fluid is a biomarker of *Aspergillus*. The diagnostic efficacy of GM testing

TABLE 3 Comparison of GMI values in BALF between the two groups

Group	No. of cases	Avg rank	Rank sum	Mann-Whitney U	Wilcoxon W	Z-value	*P* value
Control	230	120.55	27,726.00	1,161.00	27,726.00	−11.567	0.000
Case	79	255.30	20,169.00				

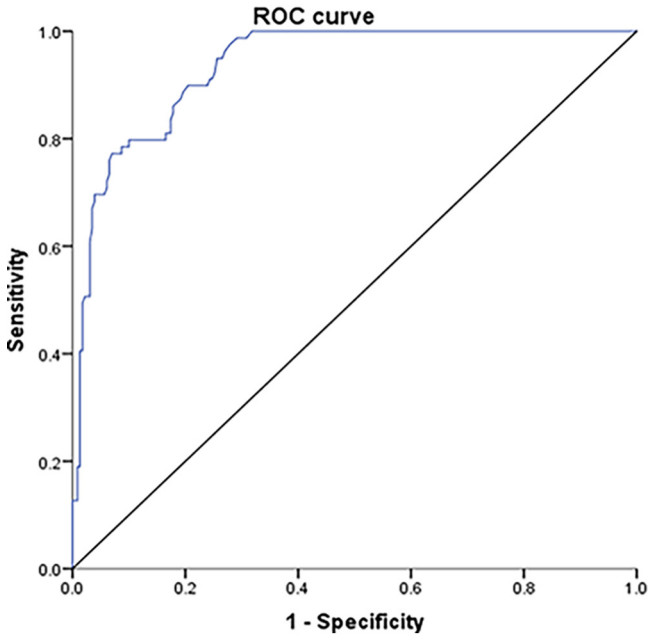

FIG 1 ROC curve.

is high, and GM is now considered a diagnostic marker for aspergillosis (10, 11). Sulahian et al. (12). reported that the results of GM tests are available 5 to 8 days earlier than those of imaging modalities.

At present, there is no standard cutoff value for the BALF GM test (12–15). In a meta-analysis of the diagnostic performance of GM, Zhou et al. (16) showed that, with cutoff values of 0.5, 0.8, and 1.0, the sensitivity was 0.75, 0.69, and 0.68 and the specificity was 0.89, 0.94, and 0.96, respectively.

The results of this study showed that when GMI is 0.5, the sensitivity and specificity of GM detection in BALF were similar to those reported in the literature (17). When the GMI values rose to 0.88 and 1.0, the specificity rose to 0.93 and 0.961, respectively, which are close to the reports at home and abroad (17, 18). In 25 patients with confirmed pulmonary aspergillosis, the index value of GM detected in BALF was greater than 0.5, and 23 cases had GMIs greater than 1.0, which may be related to the higher sensitivity and specificity of GM in BALF. When GMI is 0.5, the positive predictive value of GM detection in BALF was 0.557, and the negative predictive value was 0.966. When GMI is 0.88 or 1.0, the positive predictive value was 0.792 or 0.917, respectively, which greatly reduced the misdiagnosis rate. According to the literature report (19), the optimal cutoff value of serum GM detection is 0.5. This study suggests that the optimal cutoff value of BALF-GM is 0.88, indicating that its sensitivity is higher, which may be due to GM reflecting galactose peptide antigen release. Neutrophils can eliminate GM in the blood through the mannose-binding receptor, thereby reducing the detection rate of serum GM.

BALF GM cutoff values are set for patients with pulmonary aspergillosis with or without a variety of underlying diseases and may not be suitable for patients with chronic respiratory disease (20). Therefore, a classification system for patients with chronic respiratory diseases and pulmonary aspergillosis infection is needed, and a

TABLE 4 Area under the ROC curve

Test result variable	Area	SE	Progressive significance	Asymptotic 95% confidence interval	
				Lower limit	Upper limit
BALF GM	0.936	0.013	0.000	0.910	0.962

TABLE 5 BALF GM test diagnostic efficacy evaluation

Cutoff value	Yoden index	Sensitivity	Specificity	Positive predictive value	Negative predictive value	False positive rate	False negative rate
0.505	0.672	0.924	0.748	0.557	0.966	0.252	0.076
0.88	0.702	0.772	0.93	0.792	0.922	0.07	0.228
1.005	0.657	0.696	0.961	0.917	0.902	0.039	0.304

BALF GM cutoff value that is in line with clinical practice should be identified. In this study of patients with chronic respiratory diseases, the optimum BALF GM cutoff value for pulmonary aspergillosis was 0.88. Compared with data from previous studies (21, 22), there is a certain difference between the BALF GM value of patients with chronic airway inflammation and the BALF GM value of patients with various underlying diseases or neutropenia. It is believed that the GM test may need to be based on different underlying diseases or immunity, such as neutropenia and non-neutropenia (23, 24), organ transplantation and non-organ transplantation (25, 26), and hematological tumors (27, 28), but setting different optimal thresholds may require more research to confirm. The best cutoff value of BALF GM in pulmonary *Aspergillus* patients with different risk factors should be set according to the results of BALF GM tests, further increasing the diagnostic efficacy of BALF GM for pulmonary aspergillosis cooccurring with other conditions. For diagnosis of chronic respiratory diseases cooccurring with pulmonary aspergillosis, in addition to the BALF-GM test, the diagnostic efficacy of pathogens in BALF, GM in serum, and imaging modalities warrants further investigation. In addition, we noticed that BALF GM values was higher in some patients without *Aspergillus* infection and lower in small number patients with *Aspergillus* infection. It shows that BALF GM has certain false positives and false negatives, except common causes, such as antibiotics, cellulose membrane for hemodialysis, intravenous immunoglobulin, albumin, low *Aspergillus* burden, etc. The different recovery rates of bronchoalveolar lavage fluid should be included. Bronchoscopy and lavage procedures should be standardized to avoid false positive and false negatives. We suggest that 60 to 80 ml saline should be lavaged to a bronchial segment or subsegment several times. The recovery amount should be more than 50%, as several tubes of recovery solution were mixed for GM detection to reduce the differences, which diluted the *Aspergillus* galactomannan. Therefore, the diagnosis of pulmonary aspergillosis should be combined with clinical manifestations, treatment response, and other factors for comprehensive judgment (29).

In summary, our study demonstrates that yhe BALF GM test has diagnostic utility for chronic respiratory diseases cooccurring with pulmonary aspergillosis. We infer, for pulmonary *Aspergillus* patients, that the best cutoff value of BALF GM may be different according to different risk factors. More clinical data are needed to explore BALF GM values in patients with pulmonary *Aspergillus* under different immune conditions.

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We declare no competing interests.

P.X., G.L., C.Z., J.M., and W.-D.S. contributed to data acquisition, analysis, and interpretation. G.L. and P.X. wrote and revised the article.

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