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A multidimensional grading system for ABPA treatment escalation within the first year: The HEID score

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ABSTRACT

Background: Susceptibility to relapse is an important feature of allergic bronchopulmonary aspergillosis (ABPA); early identification of patients at high risk of relapse is urgently needed. A practical score that classifies the severity of ABPA according to its prognosis is not available.

Methods: We retrospectively reviewed patients with a diagnosis of ABPA at our hospital between January 2010 and December 2022. Logistic regression analysis was used to investigate independent risk factors for ABPA treatment escalation and select the variables included in the final score.

Results: One hundred and three patients with ABPA were enrolled in this study. An eosinophil count >1000/μL, *Aspergillus fumigatus*-specific IgE (Sp-IgE) >3.5 kUA/L, expectoration of brownish-black mucus plugs, high-attenuation mucus (HAM) and a percentage of the predicted diffusing capacity of carbon monoxide (DLCO/pred) < 60% were independent risk factors for ABPA treatment escalation. Initial treatment with antifungals was an independent protective factor. The final scale, designated HEID, incorporated 4 dichotomized variables: HAM (H, 1 point); eosinophil count (E, cutoff 1000/μL, 1 point); Sp-IgE (I, cutoff 3.5 kUA/L, 1 point) and DLCO/pred (D, cutoff 60%, 1 point). A score of 0–1 point indicated a low relapse risk; 2–4 points indicated a high relapse risk.

Conclusion: This easy-to-use multidimensional grading system was capable of accurately classifying the risk of treatment escalation in ABPA.

Keywords: Allergic bronchopulmonary aspergillosis, Relapse, Risk factors, Prognosis, Score

INTRODUCTION

Allergic bronchopulmonary aspergillosis (ABPA) is an allergic pulmonary disease caused by a hypersensitivity reaction to Aspergillus species.[1,2] A meta-analysis has shown that the prevalence of ABPA in adults with asthma worldwide ranges from 0.72% to 3.5%,[3] and 2.5% of nonsmoking adult asthma patients in China meet the diagnostic

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criteria for ABPA,[4] which reveals that ABPA is not a rare disease in asthma patients. ABPA can also occur in people with chronic obstructive pulmonary disease (COPD),[5,6] bronchiectasis[7] and even in people without obvious basic lung diseases.[8] Similar to other chronic airway diseases, such as asthma, COPD and bronchiectasis, ABPA has a significant relapse or acute exacerbation rate of approximately 19.8%–50%,[9-17] with a risk of relapse even after years of remission.[18] Patients with exacerbation often have significant clinical and radiologic worsening with increased IgE, which seriously lowers the patient's quality of life. If treatment is not escalated in a timely manner, severe airflow obstruction and destruction of lung structures, such as central bronchiectasis, may occur.[19] For chronic airway diseases such as COPD and bronchiectasis, there are already more recognized scoring systems for grading the severity or risk of relapse, such as the GOLD ABE Assessment Tool for COPD,[20] BSI and FACED score for bronchiectasis,[21,22] which can efficiently assist in developing treatment plans and determining appropriate follow-up intervals. However, for patients with ABPA, although studies have staged the natural course of ABPA in great detail and many studies have reported risk factors for the exacerbation of ABPA, an accurate and practical risk scoring system to predict the risk of relapse of ABPA is still not available. The present study developed a multidimensional score that classifies the risk of treatment escalation within 1 year after initial treatment by a retrospective investigation of patients with ABPA. We divided patients with ABPA into a high risk of escalation group and a low risk of escalation group based on their scores, thus promoting early identification and intervention of high-risk patients, timely monitoring, and adjustment of treatment to reduce the frequency of relapses and acute exacerbations to ultimately mitigate lung injury.

METHODS

Study design and ethics approval

This study was a retrospective clinical data analysis, and the research protocol was approved by the Ethics Committee of the hospital. The requirement for obtaining informed consent was waived due to the retrospective nature of the study, and we confirmed that all data were anonymized and maintained with confidentiality.

Study subjects

The medical records of patients diagnosed with ABPA in the outpatient or inpatient department of Respiratory and Critical Care Medicine from January 2010 to December 2022 in the information system of the hospital were reviewed using "allergic bronchopulmonary aspergillosis" as the search term.

Inclusion and exclusion criteria

Patients with ABPA who met the diagnostic criteria of the "Diagnostic criteria for allergic bronchopulmonary aspergillosis" by The Human and Animal Mycology (ISHAM) working group in 2013 were included in the study,[19,23] and patients with insufficient diagnostic evidence and less than 12 months of follow-up were excluded. The diagnosis of COPD complied with the diagnostic criteria of the Guidelines for the Diagnosis and Treatment of COPD (2013 Revised Edition).[24] The diagnosis of asthma complied with the diagnostic criteria of the Guidelines for the Prevention and Treatment of Bronchial Asthma (2016 Edition).[25] The diagnosis of bronchiectasis complied with the diagnostic criteria of the Expert Consensus on the Diagnosis and Treatment of Adult Bronchiectasis (2012 Edition).[26] Central bronchiectasis (CB) was defined using 2 different criteria, depending on whether bronchiectasis was confined to the medial half (point midway between the hilum and chest wall) or the medial two-thirds of the lung.

Data collection

Data, including general information, clinical manifestations, laboratory tests, chest high-resolution computed tomography (HRCT), pulmonary function (Jaeger, Germany), diagnosis course, follow-up time, and treatment medicine, were collected from the medical records of patients. Serum total immunoglobulin E (IgE) was assessed using a Roche Cobas e601 electrochemiluminescence instrument; *Aspergillus fumigatus* m3 allergen among Thermo Fisher Scientific detection reagents was used to assess *Aspergillus fumigatus*-specific IgE. The results of laboratory tests, chest HRCT, and pulmonary function were obtained when the patients were diagnosed with ABPA for the first time in our hospital or in another hospital.

Treatment

All cases initiated with treatment immediately after being diagnosed with ABPA. Patients were treated with glucocorticoids with or without an antifungal agent (itraconazole/voriconazole). The initial dose of prednisone was 0.5, and 0.25 mg/kg/day for 4 to 6 weeks each; then, it was usually tapered by 5 mg every 4 weeks and then discontinued, with the tapering rate being determined by the clinician's judgment, with a full course of treatment lasting at least 6 months. Antifungal treatment with itraconazole or voriconazole 200 mg bid was administered for at least 4 months. The duration of treatment varies according to the severity of the disease, and the total course of treatment varies from person to person.

The patients were followed up every 4 weeks for 6 months, then every 3 months, or at any time if respiratory symptoms worsened. At every visit, we monitored the patient with a physical review, peripheral blood eosinophil count, Sp-IgE and serum total IgE (HRCT only at the first visit and respiratory symptoms worsened).

Treatment escalation was defined as an increase in the dose of oral glucocorticoids or antifungal drugs, a reintroduction of glucocorticoids or antifungal drugs after discontinuation of the drug and application of the new dose for at least 1 week, or not applying glucocorticosteroids or antifungal drugs after the diagnosis of ABPA and starting treatment with oral glucocorticosteroids or antifungal drugs. All treatment escalation was under the guidance of a medical professional due to changes in the condition of the patient during the follow-up and after exclusion of an acute exacerbation of asthma and treatment escalation occurred during the following: ① worsening of clinical symptoms, such as worsening of cough, sputum, wheezing, etc; ② over 50% increase in IgE compared to the value after achieving clinical stability; ③ 20–50% increase in IgE compared to the value after achieving clinical stability; ④ increase in peripheral eosinophil counts compared to the last laboratory test; and ⑤ new infiltrating shadow on imaging test; Treatment escalation meets ①② or ①③④ or ①③⑤ at the same time. The percentage increase in serum total IgE during exacerbation was calculated as exacerbation IgE levels minus lowest IgE recorded during clinical stability (pre-exacerbation IgE) divided by the pre-exacerbation IgE.

Construction of the score

The 103 patients with ABPA were used to construct the initial score (construction cohort). Of the 8 variables that were initially selected, only those with a statistically significant capacity to predict the probability of treatment escalation in the one-year follow-up were included in the final score, except for ABPA. Once these variables were identified, they were dichotomized to facilitate the calculation of the score.

Validation of the score

We compared the area under the curve (AUC) of the prediction model and that in the internal cross validation - tenfold cross-validation of predictive model to evaluate whether the prediction model is representative.

Statistical analysis

Data were analyzed, and graphs were drawn with SPSS (version 26.0; SPSS, Chicago, IL, USA) and Stata (version 17.0). Categorical variables are expressed as numbers and percentages. Continuous variables are expressed as the mean $\pm$ standard deviation or median with interquartile range (IQR; 25th to 75th percentile). Categorical variables were compared using the chi-square test. The cutoff value of continuous variables was calculated by the Youden index, such as 1×10^9/L eosinophil count (Youden index: 1.02×10^9/L), 3.5 kUA/L Sp-IgE (Youden index: 3.52 kUA/L) and 1900IU/mL IgE (Youden index: 1913IU/mL). And 60% DLCO/pred and 50% FEV_1/pred was determined by expert consensus.[27] To identify variables independently associated with the probability of 1-year treatment escalation, we conducted logistic regression analysis by including the variables with $P \leq 0.05$ in the univariate analysis. A value of $P < 0.05$ was considered to indicate statistical significance.

RESULTS

Baseline data of patients with ABPA

The records of 124 inpatients and outpatients were retrieved, and 13 patients with an inadequate diagnosis and 8 patients with a follow-up period of

less than 12 months were excluded. Among the 103 patients, 89 patients fully met the diagnostic criteria, and the total IgE of 14 patients was not more than 1000 IU/mL (692–978.2 IU/mL). The clinical characteristics and imaging features met the diagnostic criteria of ABPA, and glucocorticoids and antifungal drugs were effective. Finally, 103 patients were included, including 47 males; There were 39 patients who were escalated to treatment for ABPA after the initial treatment within 1 year: 26 patients met ①②, 12 patients met ①③④, and 1 patient met ①③⑤ at the same time.

The mean time of initial treatment escalation was 7.0 (5.0–11.0) months after the initial treatment. The mean dosage of glucocorticosteroids before treatment escalation was 7.05 mg per day and that after treatment escalation was 19.72 mg per day. The total serum IgE at the time of treatment escalation was 1130 (572.50–2500.0) IU/mL, and the peripheral blood eosinophil count was 0.43 (0.21–0.99) $\times$ 10^9/L.

Comparison of characteristics between patients who received or did not receive treatment escalation in 1 year

The proportion, of patients with expectoration of brownish black mucus plug (BBMP), blood eosinophil count >1 $\times$ 10^9/L, Sp-IgE ≥3.5kUA/L, proportion of patients with bronchiectasis, central bronchiectasis, high attenuation mucus (HAM), proportion of patients with FEV_1/pred<50%, or DLCO/pred<60% at diagnosis were significantly higher in patients who received escalated treatment in 1 year than patients who did not receive escalated treatment in 1 year. The proportion of patients treated with antifungals was significantly lower in patients who received escalated treatment in 1 year than in patients who did not receive escalated treatment in 1 year (Table 1, Fig. 1).

Results of logistic regression analysis

We included expectoration of BBMP, eosinophil count, Sp-IgE, complicating bronchiectasis, central bronchiectasis, HAM, FEV1/pred, DLCO/pred, and antifungals in logistic regression analysis. Logistic regression analysis showed that expectoration of BBMP (OR = 6.74, 95% CI 1.12–40.66, P = 0.037), eosinophil count >1 $\times$ 10^9/L ((OR = 7.35, 95% CI 1.48–36.49, P = 0.015), Sp-IgE >3.5 kUA/L (OR = 17.34, 95% CI 2.59–116.22, P = 0.003), HAM (OR = 30.25, 95% CI 3.13–292.33, P = 0.003), and DLCO/pred <60% (OR = 52.44, 95% CI 4.63–593.79, P = 0.001) were independent risk factors associated with treatment escalation in 1 year in patients with ABPA. Treatment with antifungals (OR = 0.020, 95% CI 0.002–0.202, P = 0.001) was an independent protective factor associated with treatment escalation in 1 year in patients with ABPA. We show the results of the nomogram in Fig. 2. The AUC of the prediction model was 0.860 in the 103 patients with ABPA samples (Fig. 3A). For the Hosmer–Lemeshow test, the P value of the prediction model was 0.316 (P > 0.05) (Fig. 3B). The AUC of the prediction model was 0.780 in the internal cross validation - tenfold cross-validation of predictive model (Fig. 4A).

The multidimensional approach to ABPA: the HEID score and its simplified version

Table 2 shows the result of the logistic regression analysis without the factor of antifungals, including the 4 dichotomized and independent variables that would comprise the final HEID score: HAM (H, β = 1.712, OR (95% CI) 5.54 (1.43–21.44), p = 0.013); eosinophil count (E, β = 1.809, OR (95% CI) 6.10 (1.63–22.87), p = 0.007); Sp-IgE (S, β = 1.622, OR (95% CI) 5.06 (1.31–19.57), p = 0.019); DLCO/pred (D, β = 2.098, OR (95% CI) 8.15 (1.87–35.60), p = 0.005). The β-coefficients were rounded to the nearest whole number to simplify the final score for each variable, as shown in Table 3. To further simplify the score and facilitate clinical application, we assigned a score of 1 to all 4 variables (Table 3) and tested the difference between the area under the ROC curve with the original β values and the simplified β values. We then calculated the predictive capacity of the constructed score to determine its validity. There was no significant difference between the area under the ROC curve with the original β values and the simplified β values (0.860 vs. 0.840) (P = 0.324 > 0.05) (Fig. 4B).

DISCUSSION

Most patients with ABPA can achieve remission after standardized treatment but are susceptible to relapse after medication reduction or discontinuation.[19] Several studies have explored the

Variables	Univariate analysis				Logistics analysis	
	Treatment escalation in 1 year					
	Yes (n = 39)	No (n = 66)	HR (95%)	P value	HR (95%)	P value
Age			0.60 (0.26–1.38)	0.232		
<60 years old	26 (66.67%)	35 (54.69%)				
≥60 years old	13 (33.33%)	29 (45.31%)				
Gender			0.84 (0.38–1.86)	0.664		
Male	19 (48.72%)	34 (53.13%)				
Female	20 (51.28%)	30 (46.87%)				
Smokers			1.03 (0.44–2.41)	0.955		
Yes	13 (33.33%)	20 (31.25%)				
No	26 (66.67%)	41 (64.06%)				
BMI	22.40 (19.23–24.85)	22.86 (21.64–25.61)	0.88 (0.78–1.01)	0.061		
Comorbidity						
Asthma	34 (87.18%)	55 (85.94%)	1.11 (0.34–3.60)	0.858		
COPD	6 (15.38%)	8 (12.50%)	1.27 (0.41–3.99)	0.679		
Allergic rhinitis	11 (28.21%)	37 (56.06%)	0.45 (0.19–1.06)	0.064		
Rhinosinusitis	2 (5.13%)	2 (3.03%)	2.19 (0.3–16.3)	0.591		
Symptom						
Cough	39 (100%)	62 (96.88%)		0.265		
Expectoration of BBMP	19 (48.72%)	14 (21.88%)	3.39 (1.43–8.05)	0.006	6.74 (1.12–40.66)	0.037
Hemoptysis	6 (15.38%)	8 (12.50%)	1.25 (0.40–3.92)	0.702		
Wheezing	33 (84.62%)	57 (89.06%)	0.58 (0.17–1.94)	0.376		
Laboratory test						
Eosinophil, $\times 10^9$/L			7.01 (2.87–17.12)	<0.001	7.35 (1.48–36.49)	0.015
Eo < 1	14 (35.90%)	51 (79.69%)				

(continued)

Variables	Univariate analysis				Logistics analysis	
	Treatment escalation in 1 year					
	Yes (n = 39)	No (n = 66)	HR (95%)	P value	HR (95%)	P value
Eo ≥ 1	25 (64.10%)	13 (20.31%)				
Total IgE, IU/mL			1.12 (1.50–2.51)	0.786		
IgE<1900	16 (41.03%)	36 (56.25%)				
IgE≥1900	23 (58.97%)	28 (43.75%)				
Sp-IgE, kUA/L			4.87 (1.99–11.94)	0.001	17.34 (2.59–116.22)	0.003
Sp-IgE<3.5	9 (23.08%)	38 (59.38%)				
Sp-IgE≥3.5	30 (76.92%)	26 (40.63%)				
HRCT findings						
Bronchiectasis	35 (89.74%)	41 (64.06%)	4.91 (1.55–15.56)	0.007		
CB	22 (56.41%)	15 (23.43%)	4.23 (1.79–9.96)	0.001		
HAM	29 (74.36%)	23 (35.94%)	5.17 (2.14–12.48)	<0.001	30.25 (3.13–292.33)	0.003
Spirometry						
FEV_1pred, %			2.79 (1.04–7.44)	0.041		
<50%	13 (33.33%)	14 (21.88%)				
≥50%	13 (33.33%)	39 (60.94%)				
DLCOpred, %			4.32 (1.45–12.87)	0.009	52.44 (4.63–593.79)	0.001
<60%	11 (28.21%)	8 (12.50%)				
≥60%	14 (35.90%)	44 (68.75%)				
Initial treatment drug						
Glucocorticoids	36 (92.31%)	50 (78.13%)	3.36 (0.90–12.56)	0.072		
Antifungals	19 (48.72%)	42 (65.63%)	0.43 (0.19–0.96)	0.046	0.02 (0.002–0.202)	0.001

Table 1. (Continued) Comparative characteristics between patients who received or did not receive treatment escalation in 1 year. *Abbreviations: BBMP= Brownish black mucus plug; CB= Central bronchiectasis; COPD= Chronic Obstructive Pulmonary Disease; DLCO/pred = Percentage of diffusion capacity of carbon monoxide predicted; FEV1/pred: Percentage of FEV_1 predicted; HAM = high-attenuation mucus; IgE = Immunoglobulin E; PEF= Peak expiratory flow percentage; Sp-IgE: Aspergillus fumigatus specific IgE.*

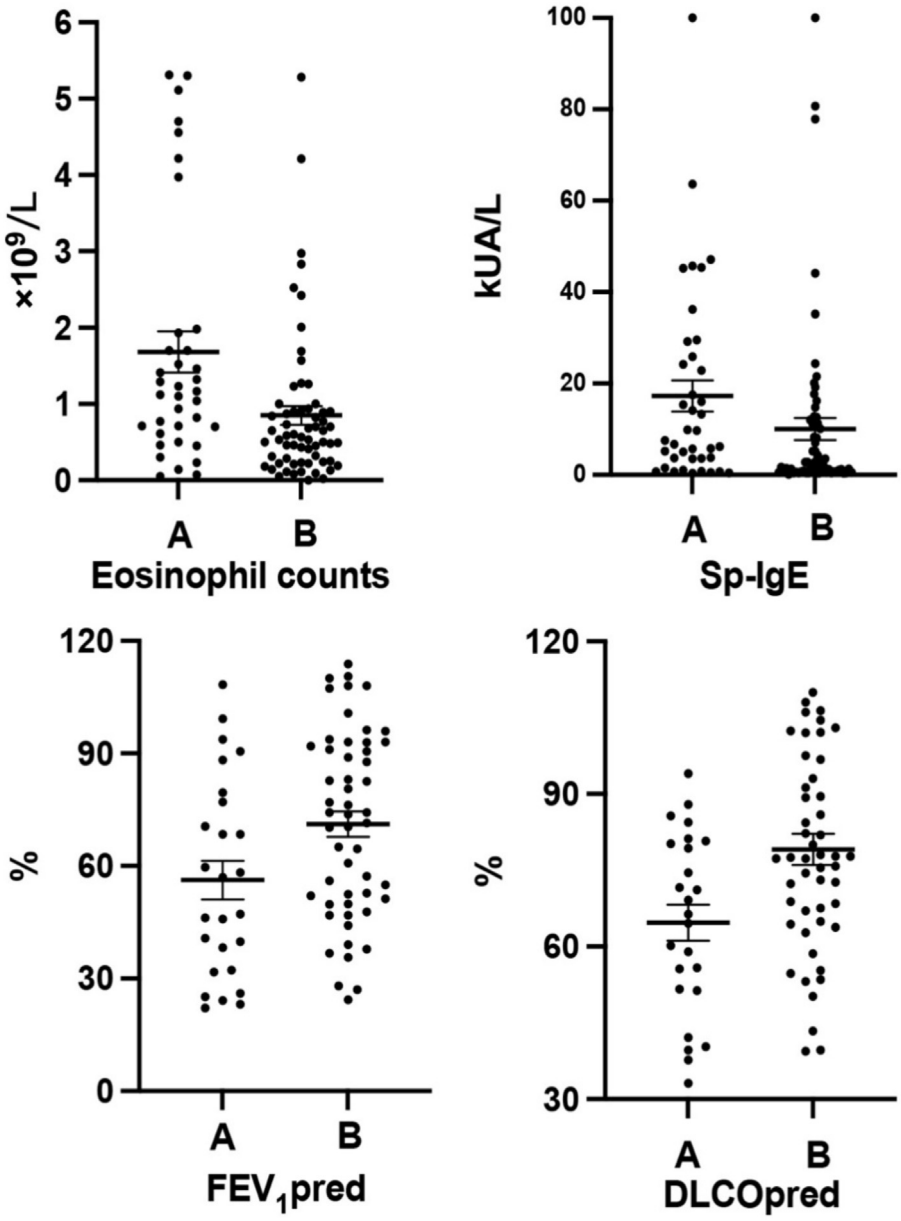

Fig. 1 Comparison of characteristics between patients who escalated treatment in 1 year and those who did not.

correlation between the clinical features of ABPA and relapse,[9-17] but there are still no uniform criteria for defining "relapse". The Human and Animal Mycology (ISHAM) working group divides ABPA into 7 stages and defines stage III exacerbation as clinical and/or radiological worsening and an increase in serum total IgE by at least 50% from the new baseline established during response/remission.[19] Some studies have defined their own criteria for ABPA relapse.[16,28] The criteria for "relapse" are not fully consistent across studies, and the follow-up time varies widely. The relapse of ABPA is usually accompanied by a change in treatment regimen. In this study, we retrospectively analyzed the changes in the treatment regimen of 103 patients diagnosed with ABPA within 1 year after receiving treatment. The included patients were followed up by professional respiratory physicians for a long period of time, and adjustments of the treatment regimen were made based on a comprehensive assessment of symptoms, serology, radiology, and exclusion of an acute exacerbation of asthma; therefore, this study used treatment escalation as a marker of relapse, which helps to identify patients at high risk of clinically significant relapse. Through

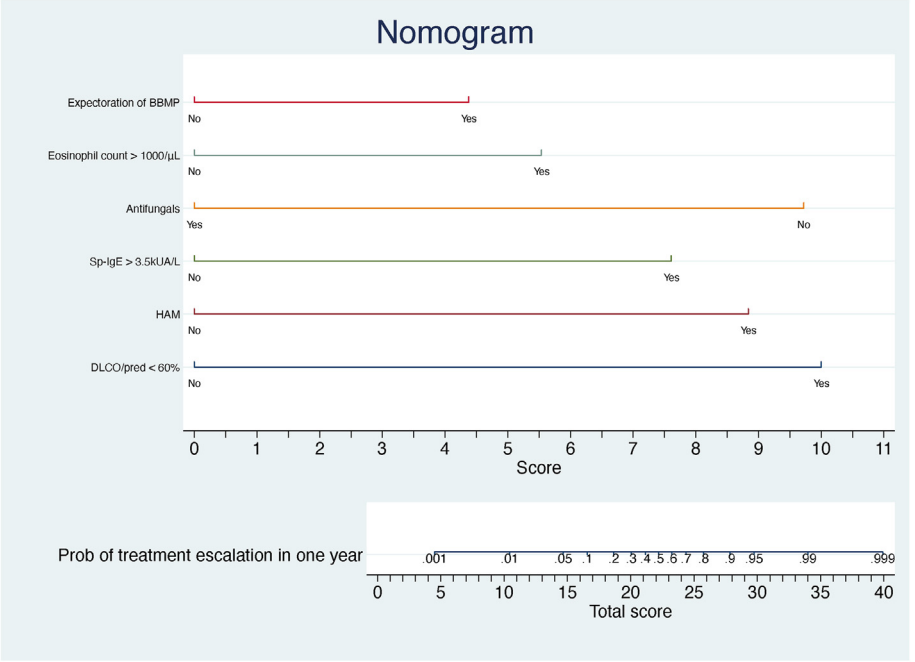

Fig. 2 A nomogram that predicts the probability of treatment escalation in 1 year.

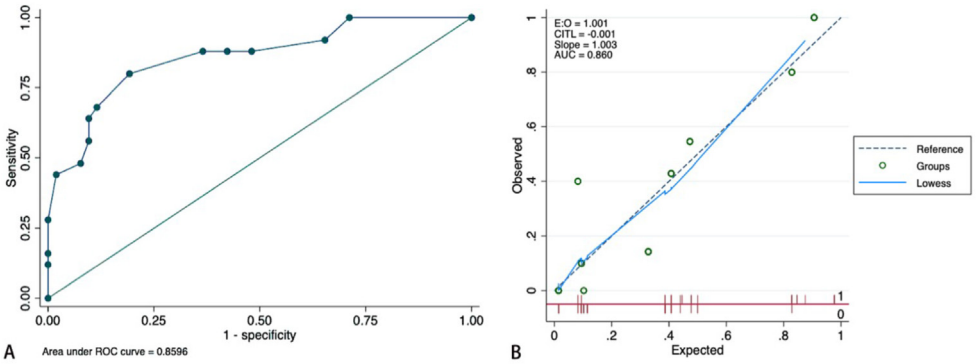

Fig. 3 A: The area under the ROC curve of the prediction model. B: The Pmcalplot of the prediction model.

logistic regression analysis, we initially determined the predictive efficiency of each significant factor and developed a score for treatment escalation to ABPA as well as a simplified version. The multidimensional grading system included 4 aspects of comorbidity, Th2 immune response indicators (peripheral blood eosinophil count, Sp-IgE), radiology features and lung function, which

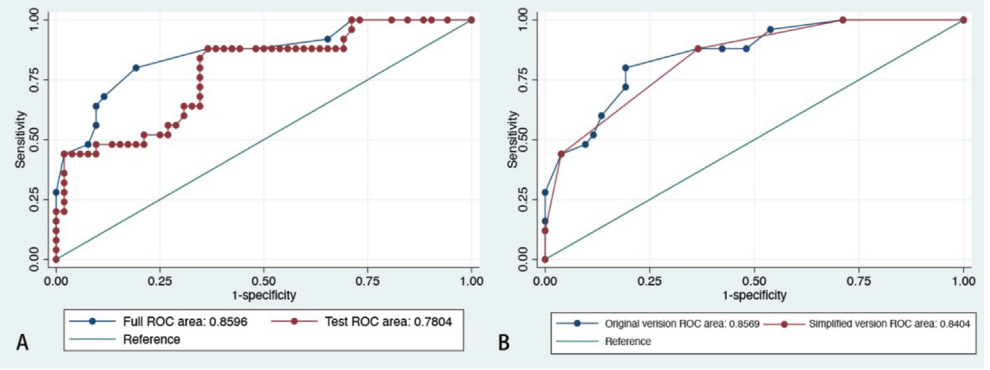

Fig. 4 A: The internal cross validation-tenfold cross-validation of predictive models. B: Comparison of the area under the ROC curve with the original β values and the simplified β values.

	OR (95%CI)	P value	β-coefficient	
			Initial	Rounded
Eosinophil count >1000/μL	6.10 (1.63–22.87)	0.007	1.809	2
HAM	5.54 (1.43–21.44)	0.013	1.712	2
Sp-IgE >3.5kUA/L	5.06 (1.31–19.57)	0.019	1.622	2
DLCOpred <60%	8.15 (1.87–35.60)	0.005	2.098	2

Table 2. Predictive capacity for treatment escalation of the different dichotomized variables included in the final score. *Abbreviations: DLCO = Diffusion capacity of carbon monoxide; HAM= High-attenuation mucus; IgE = Immunoglobulin E; Sp-IgE: Aspergillus fumigatus specific IgE.*

more comprehensively reflect the severity of ABPA. Therefore, the grading system could be used for accurately predicting the relapse risk of patients with ABPA, promoting early identification and intervention of high-risk patients, timely monitoring and adjustment of treatment, reducing the rate of relapse and ultimately mitigating lung injury.

Logistics regression analysis showed that eosinophil count >1000/μL, Sp-IgE >3.5 kUA/L, HAM, expectoration of BBMP, and DLCO/pred <60% were independent risk factors for treatment escalation to ABPA, but initial treatment with antifungals was an independent protective factor. Aspergillus colonization induces eosinophil aggregation, mucus plugging and bronchiectasis, which are key elements in the pathogenesis of ABPA. Moreover, the correlation between HAM, increased eosinophils, and central bronchiectasis with relapse of ABPA has been reported in some previous studies. Similar to HAM, expectoration of BBMP as a characteristic symptom of ABPA also represents the development of mucus plugging in the airways of patients with ABPA. Thirty-three (32.04%) of our patients had a history of BBMP, and fifty-two (50.49%) of our patients had HAM, which is comparable to previous studies.[14,29] Both are independent risk factors for relapse of ABPA, which is in line with several previous studies.[9,29–31] [14]HAM consists of mucin,[32] eosinophil extracellular traps,[33] *Aspergillus fumigatus* filaments,[33] calcium ions and other metal ions.[34] HAM is positively correlated with an increase in serum Th2 inflammatory response-related indicators (Eo, IgE, Sp-IgE).[29] Meanwhile, HAM aggravates the destruction of airway epithelium and normal lung structures, leading to bronchiectasis or pulmonary fibrosis, making it easier for Aspergillus fumigatus to colonize. The HAM group presented higher blood eosinophil cell counts, higher rates of Aspergillus detection isolated in sputum and expectoration of BBMP, more affected lobes and segments, and poorer pulmonary function (FEV1%, PEF%), which forms a vicious cycle that makes the disease difficult to control and increases the likelihood of relapse.

Variable	Points	Points (Simplified version)
HAM		
No	0	0
Yes	2	1
Eosinophil count >1000		
No	0	0
Yes	2	1
sIgE >3.5		
No	0	0
Yes	2	1
DLCOpred <60%		
No	0	0
Yes	2	1

Table 3. Final score, cutoff points of the dichotomized variables and scoring of each variable and Simplified version of the HEID score. *Abbreviations: DLCO = Diffusion capacity of carbon monoxide; HAM = high-attenuation mucus; IgE = Immunoglobulin E; Sp-IgE: Aspergillus fumigatus specific IgE.Low-risk group: ≤1points, high-risk group: 2–4 points.*

Eosinophils are considered important inflammatory cells in the genesis and development of ABPA. In 1 series, 75% of the patients had a count >500 cells/μl, while 40% of the patients had an eosinophil count

of >1000 cells/μl.[35] Eosinophils can release massive amounts of cationic proteins and mobilize proinflammatory cytokines, including interleukin 6 and interleukin 8, to damage the airway epithelium. Eosinophils also increase the viscosity of airway secretions by secreting extracellular traps,[36] thereby exacerbating mucus embolism, fungal colonization and inflammation in the airway. Agarwal found that peripheral blood eosinophil count ≥1000 cells/μL independently predicted ABPA exacerbation.[37] Previous studies have demonstrated that increased eosinophil levels are associated with complicating central bronchiectasis, while HAM and frequent relapses[29,30] were also independent risk factors for relapse of ABPA.[14]

There are few studies on the influence of Sp-IgE and lung function on ABPA relapse. An elevated level of serum Sp-IgE (>0.35 kUA/l) is currently the most sensitive biomarker for the diagnosis of ABPA,[38] but it has limited utility in dynamically monitoring treatment responses and relapse of ABPA in previous studies.[39] Sp-IgE is produced locally in the lung, while the production of total IgE in ABPA occurs in the peripheral immune system,[40] which weakens its power to monitor the follow-up of patients with ABPA. However, the present study found a prominent effect of Sp-IgE levels at diagnosis on the long-term prognosis of ABPA. Increased Sp-IgE may be associated with the presence of more Aspergillus fumigatus-specific antigens in the airway, which also implies a heavier fungal load in the airway. Various Aspergillus fumigatus-specific antigens can damage airway cells, including direct toxicity to cells as well as protease hydrolysis.[41,42] Although Sp-IgE levels are not an ideal indicator for dynamically monitoring treatment responses in ABPA, more studies investigating the utility of predicting the risk for relapse of ABPA are warranted.

DLCO/pred was important in assessing the severity and exacerbation risk of chronic airway diseases such as COPD and interstitial lung disease.[43–45] However, the importance of DLCO in ABPA assessment has not received enough attention. Reduced DLCO/pred was not rare in patients with ABPA. We previously found that DLCO/pred was significantly lower in patients who had ABPA with COPD and in the death group.[46] Zeng et al reported that the ABPA-CB group had a lower DLCO and a higher rate of recurrence,[30] and the present study strongly recommended DLCO/pred as a value in the score that predicts the risk of relapse of ABPA. Although the exact cause of diffusion impairment in patients with ABPA is not entirely clear, early diffusion capacity screening should be strengthened to identify high-risk patients.

Central bronchiectasis is a classic finding in ABPA. Previous studies suggested that patients with ABPA and CB have higher levels of total IgE and Sp-IgE, more severe immunoreactivity, poorer lung function (forced vital capacity (FVC) and DLCO), and more frequent exacerbations,[30] a finding consistent with this study and our previous study.[46] In this research, only univariate analysis showed a noteworthy increase in the rate of complicating CB in patients with treatment escalation within 1 year, and regular follow-up of ABPA patients with CB should be strengthened to adjust treatment in a timely manner and reduce further damage to the airway from frequent exacerbations.

The combination of initial treatment with antifungal therapy decreases the rate of acute exacerbations, which has been reported in several previous studies and is also consistent with the results of this study.[12,13,47] Antifungal therapy reduces the fungal load in the airways, which helps to alleviate symptoms in the acute phase of ABPA and reduce the recurrence rate. The treatment escalation prediction model in this study showed that initial treatment combined with antifungal agents markedly decreased the rate of treatment escalation within 1 year. Since the scoring system is designed to assess the risk of relapse in patients before initial treatment and does not include treatment regimens that did not occur as indicators of impact, we did not include whether initial treatment was combined with antifungal agents in the logistic test. However, the role of antifungal therapy in the initial treatment of ABPA and in the treatment after relapse should be emphasized.

As ABPA is increasingly and widely diagnosed and treated around the world, it is essential to construct a score that pinpoints the risk of relapse of ABPA more effectively than any single variable by embracing the various clinical, serological, radiological and functional aspects characteristic

of ABPA. To our knowledge, this is the first scoring system that predicts the risk of relapse of ABPA globally. This study presents the construction of a scoring system that is easy to calculate, obtain and interpret while also covering all the aspects mentioned above. The score's multidimensional nature and the ease with which it can be obtained and interpreted are noteworthy, as it covers the main fields typical of patients with ABPA. On account of its assemblage of different key aspects of ABPA, the score showed excellent predictive power by an outstanding sensitivity (87.18%) and an acceptable specificity (62.5%). All the strengths above make it an attractive clinical tool. More attention should be given to patients with a high risk of relapse based on the HEID score to regularly monitor and adjust treatment to reduce relapse and acute exacerbations and improve prognosis.

However, our study had some limitations that should be acknowledged. It was a single-center retrospective study with a small sample size. We did not set an external validation cohort to confirm the score's validity. Moreover, this study investigated the correlation between clinical data at the time of first diagnosis and the risk of treatment escalation in patients with ABPA and did not include the impact of compliance, the presence of repeated exposures to allergens, and the application of novel biologically targeted drugs such as the anti-IgE antibody omalizumab on treatment escalation during subsequent follow-up. In addition, due to the lack of patients with cystic fibrosis in China, our study did not include patients with ABPA who had cystic fibrosis as a predisposing condition. Besides, although we performed sinus CT in 21 patients, of whom 1 reported nasal polyps and 19 reported sinusitis, we do not routinely perform sinus CT in patients with a definitive diagnosis of ABPA. Therefore, the combined nasal disease was not included in the analysis. Finally, although we believe that treatment escalation is a more accurate comprehensive indicator of disease progression, this indicator is not yet widely used. Multicenter studies are also needed to verify the application of this indicator.

The easy-to-use multidimensional grading system-HEID score has proven capable of accurately classifying the risk of treatment escalation in patients with ABPA. More attention should be given to the "high relapse risk ABPA" category in the HEID score, to ensure regular monitoring and adjustment of treatment in order to reduce relapse and acute exacerbations, thereby improving prognosis.

Abbreviations

ABPA: Allergic Bronchopulmonary Aspergillosis; BBMP: Brownish black mucus plug; CB: Central bronchiectasis; COPD: Chronic obstructive pulmonary disease; DLCO: Diffusion capacity of carbon monoxide; DLCO/pred: Percentage of DLCO predicted; FEV_1: Forced expiratory volume in 1 s; FEV_1/pred: Percentage of FEV_1 predicted; FVC: Forced vital capacity; HAM: High-attenuation mucus; HRCT: High-resolution computed tomography; IgE: Immunoglobulin E; PEF: Peak expiratory flow percentage; Sp-IgE: Aspergillus fumigatus-specific IgE; Th2: T helper cell type 2

Availability of data and materials

Not applicable.

Author contributions

Ma Yanliang takes responsibility for the content of this manuscript, including the data and analysis. Zhang Ping'an and Zhang Moqin contributed to the concept and design of study. Zhang Ping'an, Chen Xi, Ma Yifan and Yang Luyang contributed to the acquisition of data. Zhang Ping'an, Chen Xi, Ma Yifan and Yang Luyang contributed to the analysis of data. Zhang Ping'an contributed to the drafting of the manuscript. Gao zhancheng contributed to the revision of manuscript critically for important intellectual content. All authors approved the final manuscript.

Ethics statement

This study was a retrospective clinical data analysis, and the research protocol was approved by the Ethics Committee of Peking University People's Hospital.

Authors' consent for publication

All authors agreed to the publication of this work in the World Allergy Organization Journal.

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Declaration of competing interest

All the authors do not have any possible conflicts of interest.

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