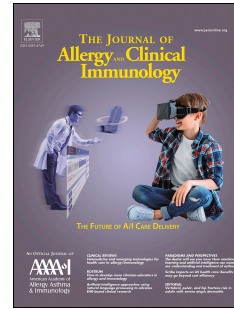


Journal Pre-proof

New Clinical Diagnostic Criteria for Allergic Bronchopulmonary Aspergillosis/Mycosis and its Validation

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PII: S0091-6749(20)31240-9

DOI: <https://doi.org/10.1016/j.jaci.2020.08.029>

Reference: YMAI 14737

To appear in: *Journal of Allergy and Clinical Immunology*

Received Date: 26 May 2020

Revised Date: 9 August 2020

Accepted Date: 17 August 2020

Please cite this article as: Asano K, Hebisawa A, Ishiguro T, Takayanagi N, Nakamura Y, Suzuki J, Okada N, Tanaka J, Fukutomi Y, Ueki S, Fukunaga K, Konno S, Matsuse H, Kamei K, Taniguchi M, Shimoda T, Oguma T, Japan ABPM research program, New Clinical Diagnostic Criteria for Allergic Bronchopulmonary Aspergillosis/Mycosis and its Validation, *Journal of Allergy and Clinical Immunology* (2020), doi: <https://doi.org/10.1016/j.jaci.2020.08.029>.

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Revised manuscript**New Clinical Diagnostic Criteria for Allergic Bronchopulmonary
Aspergillosis/Mycosis and its Validation**

Koichiro Asano, MD¹, Akira Hebisawa, MD, PhD², Takashi Ishiguro, MD, PhD⁴, Noboru Takayanagi, MD, PhD⁴, Yasuhiko Nakamura, MD, PhD², Junko Suzuki, MD³, Naoki Okada, MD¹, Jun Tanaka, MD¹, Yuma Fukutomi, MD, PhD⁵, Shigeharu Ueki, MD, PhD⁶, Koichi Fukunaga, MD, PhD⁷, Satoshi Konno, MD, PhD⁸, Hiroto Matsuse, MD⁹, Katsuhiko Kamei, MD¹⁰, Masami Taniguchi, MD⁵, Terufumi Shimoda, MD¹¹, Tsuyoshi Oguma, MD¹, and Japan ABPM research program

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43 Sources of Support

44 This study was funded by the Research Grant on Allergic Disease and Immunology,
45 from the Japan Agency for Medical Research and Development, under the grant
46 numbers JP18ek0410026 and JP20ek0410055.

47

48 Conflicts of Interest

49 Dr. Asano reports grants from Japan Agency for Medical Research and Development,
50 personal fees from Thermo Fisher Diagnostics K.K. during the conduct of the study;
51 personal fees from AstraZeneca K.K., personal fees from GlaxoSmithKline K.K., grants
52 and personal fees from Nippon Boehringer Ingelheim Co., Ltd., grants and personal
53 fees from Novartis Pharma K.K., personal fees from Teijin Pharma Ltd., grants and
54 personal fees from Sanofi S. A. outside the submitted work; Dr. Hebisawa reports grants
55 from Japan Agency for Medical Research and Development during the conduct of the
56 study; Dr. Suzuki reports grants from Japan Agency for Medical Research and
57 Development during the conduct of the study; Dr. Fukutomi reports grants from Japan
58 Agency for Medical Research and Development during the conduct of the study;
59 personal fees from Thermo Fisher Diagnostics K.K., grants and personal fees from
60 Novartis Pharma K.K., personal fees from Torii Pharmaceutical Co., Ltd, personal fees
61 from KYORIN Pharmaceutical Co., Ltd., grants from GlaxoSmithKline K.K. outside the
62 submitted work; Dr. Ueki reports grants and personal fees from Novartis Pharma K.K.,
63 grants from Japan Allergy Foundation, grants from Charitable Trust Laboratory
64 Medicine Research Foundation of Japan, grants from Japan Society for the Promotion
65 of Science KAKENHI, grants and personal fees from AstraZeneca K.K., grants from
66 Maruho Co. Ltd, grants from Mochida Memorial Foundation for Medical and

67 Pharmaceutical Research, grants from Japanese Society of Laboratory Medicine Fund
68 for Promotion of Scientific Research, personal fees from GlaxoSmithKline K.K., grants
69 and personal fees from Sanofi, grants from Japan Agency for Medical Research and
70 Development during the conduct of the study; Dr. Fukunaga reports grants from Japan
71 Agency for Medical Research and Development during the conduct of the study; Dr.
72 Konno reports grants from Japan Agency for Medical Research and Development
73 during the conduct of the study; grants from AstraZeneca K.K., grants from Novartis
74 Pharma K.K., grants from Nippon Boehringer Ingelheim Co., Ltd., grants from Japan
75 Allergy Foundation, grants from KYORIN Pharmaceutical Co., Ltd. outside the
76 submitted work; Dr. Matsuse reports grants from Japan Agency for Medical Research
77 and Development, during the conduct of the study; personal fees from Novartis,
78 personal fees from MSD K.K., personal fees from AstraZeneca K.K., personal fees from
79 Astellas Pharma Inc., personal fees from Nippon Boehringer Ingelheim Co., Ltd.,
80 personal fees from GlaxoSmithKline K.K., personal fees from KYORIN Pharmaceutical
81 Co., Ltd., outside the submitted work; Dr. Kamei reports grants from Japan Agency for
82 Medical Research and Development, during the conduct of the study; Dr. Taniguchi
83 reports grants from Japan Agency for Medical Research and Development during the
84 conduct of the study; Dr. Shimoda reports grants from Japan Agency for Medical
85 Research and Development during the conduct of the study; Dr. Oguma reports grants
86 from Japan Agency for Medical Research and Development during the conduct of the
87 study.

88

89 **Key messages**

- 90 ✓ New diagnostic criteria for allergic bronchopulmonary mycosis (ABPM) in
91 non-cystic fibrosis patients, consisting of ten components, are proposed and
92 validated.
- 93 ✓ The new criteria showed high sensitivity and specificity for ABPM, which improved
94 on the previous criteria proposed by Rosenberg and Patterson, and by the
95 International Society for Human and Animal Mycology.
- 96 ✓ The new criteria are useful both for *Aspergillus* and non-*Aspergillus* ABPM.

97

98 **Capsule Summary**

99 New diagnostic criteria for allergic bronchopulmonary aspergillosis/mycosis in
100 non-cystic fibrosis patients, consisting of ten components, show higher sensitivity and
101 specificity than the previously proposed criteria.

102

103 **Key Words**

104 Allergic bronchopulmonary aspergillosis; Allergic bronchopulmonary mycosis;
105 *Aspergillus*; Diagnosis; Eosinophils; Fungus; IgE; Mucus plugs; Severe asthma with
106 fungal sensitization

107

108 **List of Abbreviations**

109 Allergic bronchopulmonary aspergillosis: ABPA

110 Allergic bronchopulmonary mycosis: ABPM

111 Area under the curve: AUC

112 Computed tomography: CT

113 International Society for Human and Animal Mycology: ISHAM

114 Receiver operation characteristics: ROC

115

116

117 **Abstract** (236 words)

118 **Background:** There are several clinical diagnostic criteria for allergic
119 bronchopulmonary aspergillosis (ABPA). However, these criteria have not been
120 validated in detail, and no criteria for allergic bronchopulmonary mycosis (ABPM) is
121 currently available.

122 **Objective:** We propose new diagnostic criteria for ABPA/ABPM, consisting of ten
123 components, and compare its sensitivity and specificity to existing methods.

124 **Methods:** Rosenberg-Patterson's criteria proposed in 1977, International Society for
125 Human and Animal Mycology (ISHAM) criteria proposed in 2013, and our new criteria,
126 were applied to 79 cases with pathological ABPM and the control population with
127 allergic mucin in the absence of fungal hyphae (n = 37), chronic eosinophilic pneumonia
128 (n = 64), *Aspergillus*-sensitized severe asthma (n = 26), or chronic pulmonary
129 aspergillosis (n = 24). These criteria were also applied to the 179 cases with
130 physician-diagnosed ABPA/ABPM in a nation-wide Japanese survey.

131 **Results:** The sensitivity for pathological ABPM with Rosenberg-Patterson criteria,
132 ISHAM criteria, and our new criteria were 25.3%, 77.2%, and 96.2%, respectively. The
133 sensitivity for physician-diagnosed ABPA/ABPM were 49.2%, 82.7%, and 94.4%,
134 respectively. The area under the curve for the receiver operation characteristic curve
135 was 0.85, 0.90, and 0.98 for Rosenberg-Patterson criteria, ISHAM criteria, and the new
136 criteria, respectively. The sensitivity for ABPM cases that were culture-positive for
137 non-*Aspergillus* fungi, were 14.3%, 47.6%, and 90.5% with Rosenberg-Patterson
138 criteria, ISHAM criteria, and the new criteria, respectively.

139 **Conclusion:** The new diagnostic criteria showed better sensitivity and specificity for
140 diagnosing ABPA/ABPM, compared with existing criteria.

141

142 Introduction

143 Allergic bronchopulmonary aspergillosis (ABPA) was first reported by Hinson et al. ¹ as
144 bronchopulmonary aspergillosis characterized by bronchitis, eosinophilia,
145 bronchiectasis and/or mucus plugs, and the presence of *Aspergillus fumigatus* in the
146 lungs. Subsequent studies showed that ABPA pathogenesis is associated with type I
147 and III hypersensitivity reactions to *A. fumigatus* inhaled and colonized in the bronchi,
148 based on high serum IgE levels, immediate cutaneous hypersensitivity reaction with or
149 without an Arthus reaction, and presence of IgE, IgG, and/or precipitating *A.*
150 *fumigatus*-specific antibodies.²⁻⁵ In addition to *A. fumigatus*, other *Aspergillus* species
151 like *A. flavus* and *A. niger*, and other filamentous fungi like *Penicillium* and
152 *Schizophyllum commune*, can cause similar pathologies called allergic
153 bronchopulmonary mycosis (ABPM).^{6,7}

154 Rosenberg, Patterson, and their colleagues ⁵ proposed the first diagnostic criteria for
155 ABPA in 1977, which included seven primary components (asthma, peripheral blood
156 eosinophilia, positive immediate cutaneous hypersensitivity to *Aspergillus* antigen,
157 presence of precipitating antibody to *Aspergillus* antigen, increased total serum IgE
158 levels, transient or fixed pulmonary opacities, and central bronchiectasis) and three
159 secondary components (isolation of *A. fumigatus* in sputum, history of expectoration of
160 brownish plug or flecks, and Arthus-type reactivity to *Aspergillus* antigen). Later,
161 Greenberger et al. ⁴ added *A. fumigatus*-specific IgE and IgG to these criteria. Criteria
162 for patients with cystic fibrosis as a predisposing condition were proposed in 2003 ⁸,
163 consisting of high total serum IgE levels, immediate skin reactivity to *Aspergillus* antigen
164 or specific IgE, precipitating antibody or IgG to *Aspergillus* antigen, and any typical
165 radiographic findings like pulmonary infiltrates, mucus plugs, or central bronchiectasis.
166 Based on these preceding studies, the International Society for Human and Animal
167 Mycology (ISHAM) proposed new diagnostic criteria in 2013 ², which defines asthma or
168 cystic fibrosis as predisposing conditions and included two obligatory criteria: 1)
169 immediate cutaneous hypersensitivity to *Aspergillus* antigen or elevated IgE levels
170 against *A. fumigatus*, and 2) elevated total IgE levels. They also included three minor
171 criteria, at least two of which should be satisfied for ABPA diagnosis, namely: a)
172 presence of precipitating or IgG antibodies to *A. fumigatus*, b) radiographic features in
173 the lungs consistent with ABPA, and c) peripheral blood eosinophilia.

174 However, pulmonary/allergy specialists consider a substantial proportion of cases with
175 clinical ABPA do not fulfill the diagnostic criteria. Agarwal et al.⁹ examined the sensitivity
176 of an eight-component criteria, consisting of presence of *A. fumigatus*-specific IgE and
177 seven primary components in Rosenberg-Patterson criteria. They found that only 39%
178 of the cases with clinical ABPA checked at least seven of the eight components. In a
179 nation-wide Japanese survey¹⁰, 22% of 148 patients with physician-diagnosed ABPA
180 accompanied by high attenuation mucus in the central bronchi, a highly compatible
181 feature with ABPA/ABPM¹¹, lacked either the asthma or cystic fibrosis necessary for
182 ABPA diagnosis with existing criteria. Owing to the difficulty of differential diagnosis,
183 some researchers have proposed allergic fungal airway disease as an inclusive disease
184 concept encompassing severe asthma with fungal sensitization and ABPA¹².

185 Diagnosis of non-*Aspergillus* ABPM is more challenging as traditional criteria^{2,4,5} are
186 specific to ABPA caused by *A. fumigatus*, with no diagnostic criteria available for ABPM.
187 Laboratory tests for specific IgE/IgG are not necessarily present for the ABPM-causing
188 fungi, and clinical ABPM characteristics are often atypical. Ishiguro et al.¹³ reported 17
189 cases with biopsy-confirmed ABPM and finding that seven cases lacked asthma or
190 cystic fibrosis, seven cases lacked peripheral blood eosinophilia, and three cases had
191 <1,000 IU/mL total serum IgE.

192 The Japan ABPM research program, supported by the Japan Medical Research and
193 Development Organization, developed new ten-component diagnostic criteria for
194 ABPA/ABPM in non-cystic fibrosis patients (Table 1). We compared the sensitivity and
195 specificity of the new and conventional criteria to discriminate pathological and
196 physician-diagnosed ABPA/ABPM from related diseases, including fungus-negative
197 mucoid impaction in bronchi, chronic eosinophilic pneumonia, fungus-sensitized severe
198 asthma, and chronic pulmonary aspergillosis.

199

200 **Methods**

201 *Clinical diagnostic criteria for ABPM*

202 The new diagnostic criteria for ABPM are presented in Table 1. Current or previous
203 physician-diagnosed asthma or asthma-like symptoms, including wheezing, is required
204 for component #1. Peripheral blood eosinophil counts and serum IgE levels at the
205 diagnosis or recent peak values can be used for components #2 and #3. The fungal
206 type for component #5 (precipitating antibody or IgG) must be matched at the genus
207 level with component #4 (immediate cutaneous hypersensitivity or IgE). Component #6
208 (positive fungal culture) can be counted when the same fungal genus for serum tests
209 (component #4 and/or #5) was identified in culture. Component #6 can be counted if
210 there were no positive serum tests, but with a positive fungal culture. Components
211 #4-#6 are applicable for filamentous fungi, but not for yeast-like fungi like *Candida* and
212 *Saccharomyces*. Mucus plugs obtained by expectoration or by bronchoscopy can be
213 used for pathological examinations (component #7). Components #8 - #10 are
214 radiological findings, but bronchoscopy identification or expectoration history is
215 applicable for mucus plugs in component #9. High attenuation mucus (component #10)
216 is defined as mucus plugs with visually higher densities than paravertebral muscles on
217 HRCT¹¹. Patients who checked six or more of these components were diagnosed with
218 definite ABPM, and those who checked five components were diagnosed with probable
219 ABPM.

220 The criteria proposed by Rosenberg, Patterson, et al. (1977)⁵ and ISHAM², which were
221 originally specific for ABPA, were modified for cases with non-*Aspergillus* ABPM (Tables
222 E1 and E2 in Online Repository). For Rosenberg-Patterson criteria, cases satisfying all
223 seven primary components are considered as definite ABPM, and cases fulfilling six
224 primary components, except for central bronchiectasis, were designated as probable
225 ABPM. Cases satisfying ISHAM criteria in the absence of predisposing conditions
226 (asthma or cystic fibrosis), are considered as probable ABPM.

227

228 *Subjects with pathological ABPM and control diseases*

229 Mucus plugs expectorated in sputum or obtained by aspiration with bronchoscopy were
230 routinely examined microscopically by pathologists experienced with diagnosis of
231 allergic fungus-related lung diseases, in two institutes (National Hospital Organization
232 Tokyo National Hospital and Saitama Cardiovascular and Respiratory Center).

233 Pathological ABPM was diagnosed based on the presence of fungal hyphae in the
234 eosinophilic mucus plugs (allergic mucin)¹⁴. Fungal hyphae was determined using a
235 fluorescent dye (Fungiflora Y, Alfresa Pharma, Osaka, Japan), or Grocott staining.
236 Cases with intrabronchial allergic mucin lacking fungal hyphae, even after an extensive
237 survey by the pathologists, were used as a control group. The second control group
238 included patients with chronic eosinophilic pneumonia without culture-positive fungi in
239 either sputum or bronchoalveolar lavage fluid. The third control group included subjects
240 with severe asthma and fungal sensitization¹⁵ specifically sensitized to *A. fumigatus* for
241 this analysis. Severe asthma with *A. fumigatus* sensitization was defined as severe
242 asthma: 1) requiring Global Initiative for Asthma¹⁶ step 4 or 5 treatment, under the
243 management by certified pulmonologists, 2) positive for specific IgE to *A. fumigatus*
244 antigen, and 3) without fulfilling ABPA criteria proposed by Rosenberg, Patterson, et al.⁵.
245 The fourth control group included patients with chronic pulmonary aspergillosis who
246 presented with: 1) typical radiological features and 2) positive sputum culture of
247 *Aspergillus* species and/or precipitating antibodies to *A. fumigatus*.
248 Clinical and radiographic data were retrospectively reviewed in the medical charts. This
249 study was approved by the Institutional Review Boards of Tokai University School of
250 Medicine (#16R-239), National Hospital Organization Tokyo National Hospital
251 (#190033), Saitama Cardiovascular and Respiratory Center (#2019028), and National
252 Hospital Organization Sagamihara Hospital (#2019-030) and was implemented in
253 compliance with the Declaration of Helsinki. The need for informed patient consent was
254 waived by the Institutional Review Boards for this study, given the anonymity of the data
255 and the retrospective observational nature of the study.

256

257 *Subjects with physician-diagnosed ABPM*

258 A retrospective, cross-sectional survey of ABPM in Japan was performed in 2013.¹⁰ This
259 study was approved by the Institutional Review Board of Tokai University School of
260 Medicine (#13R-105), and it was implemented in compliance with the Declaration of
261 Helsinki. A total of 499 cases of physician-diagnosed ABPM were reported from 132
262 clinical centers certificated by the Japanese Respiratory Society and/or the Japanese
263 Society of Allergology. Clinical, laboratory, and radiological parameters at ABPM
264 diagnosis were evaluated in the physician-questionnaire. Cases without appropriate
265 data for peripheral blood eosinophil counts, total serum IgE levels, fungus-specific IgE

266 or immediate cutaneous reactions, fungus-specific IgG or precipitating antibody, and
267 thoracic computed tomography (CT) scan data were excluded from the analysis.

268

269 *Statistical analysis*

270 Numerical data were expressed as mean and standard deviation or median and
271 interquartile range, while categorical data were presented as numbers with respective
272 percentages. Numerical data were analyzed using the Mann-Whitney's U test or
273 Kruskal-Wallis test, while categorical data were analyzed using Fisher's exact test.
274 Receiver operation characteristics (ROC) curve analysis and area under the curve
275 (AUC) was used to compare the accuracy of the different diagnostic criteria.

276 Data of cases with pathological ABPM and physician-diagnosed disease were merged
277 for the subgroup analyses to examine the sensitivity of the diagnostic criteria in
278 non-asthmatic patients and the cases with non-*Aspergillus* ABPM. Since data for
279 pathological examination of mucus plugs were not available for cases with
280 physician-diagnosed ABPM, component #7 (positive fungal hyphae in mucus plugs)
281 was excluded from the new diagnostic criteria for these analyses.

282 The statistical analyses were performed using GraphPad Prism ver.5.0 (GraphPad
283 Software Inc., La Jolla, CA, USA). P values <0.05 were considered statistically
284 significant.

285

286 **Results**

287 *Pathological ABPM*

288 One hundred sixteen cases with eosinophilic mucus plugs in the lower airways were
289 enrolled from two institutes. A total of 79 cases (68%) presenting with fungal hyphae in
290 the mucus plugs were diagnosed as pathological ABPM. Demographic and laboratory
291 data of the cases with pathological ABPM are presented in Table 2. Mucus plugs were
292 obtained under bronchoscopy in 97% of the cases, while sputum-derived samples were
293 examined in two cases. Filamentous fungi, including *Aspergillus spp.*, *S. commune*,
294 *Penicillium spp.*, were culture-positive in 40 (49%), six (7%), and four cases (5%),
295 respectively. Demographic and laboratory data were relatively consistent, irrespective of
296 the institute, as demonstrated in Tables E3 (Online Repository), but differences were
297 present between the institutes in the prevalence of non-*Aspergillus* fungi isolation and
298 some radiographic findings (central bronchiectasis and mucus plugs in the bronchi).
299 Eleven cases with pathological ABPM checked all seven components of modified
300 Rosenberg-Patterson criteria. Nine other cases fulfilled six criteria, except for central
301 bronchiectasis. Therefore, 25.3% of the cases with pathological ABPM could be
302 diagnosed as ABPM, according to the criteria (Figure 1A). ISHAM criteria were fulfilled
303 in 61 cases (77.2%), but 24 cases (30.4%) did not present with predisposing conditions
304 and were defined as probable cases. Using the new diagnostic criteria, 71 cases
305 (89.9%) were diagnosed as definite ABPM and 5 cases (6.3%) as probable ABPM
306 (Figure 1A).

307

308 *Physician-diagnosed ABPM*

309 Appropriate clinical, laboratory, and radiologic data were available in 179 of the cases
310 with possible ABPA/ABPM reported in the nation-wide survey. Data for fungal culture
311 and radiographic findings on mucus plugs were missing in 70 (39%) and 35 cases
312 (19%), respectively. Pathological examination of mucus plugs was not performed in any
313 physician-diagnosed ABPM cases. Demographic data are presented in Table 2. There
314 were no differences in age, gender, total serum IgE levels, positive rate of
315 fungus-specific type I hypersensitivity and fungus culture between pathological and
316 physician-diagnosed ABPM. Asthma prevalence, peripheral blood eosinophil counts,
317 and positive rate of fungus-specific type III hypersensitivity were higher in patients with
318 physician-diagnosed ABPM.

319 Diagnosis of definite ABPM was made with the new diagnostic criteria in 143 cases
320 (79.9%). An additional 26 cases (14.5%) were diagnosed as probable ABPM. Therefore,
321 the sensitivity of the new criteria for definite/probable ABPM was 94.4%, and the
322 sensitivity for definite/probable ABPM with Rosenberg-Patterson criteria and ISHAM
323 criteria were 49.2% and 82.7%, respectively (Figure 1B).

324

325 *Control population*

326 Among 116 cases with eosinophilic mucus plugs, 37 cases (32%) were negative for
327 fungal hyphae, even with extensive examination by experienced pathologists.
328 Demographic data are presented in Table 3. All but one case presented with asthma.
329 Among these cases, two (5.4%), four (10.8%), and four (10.8%) cases were diagnosed
330 as ABPM based on modified Rosenberg-Patterson criteria, ISHAM criteria, and the new
331 criteria, respectively (Table 4). Another three cases (8.1%) were diagnosed as probable
332 ABPM using the new criteria.

333 Approximately half of the cases with chronic eosinophilic pneumonia (n = 64) exhibited
334 asthma. A substantial proportion (23%) of the patients with this condition showed mucus
335 plugs in the bronchi. No case presented with high attenuation mucus. No case in this
336 population fulfilled Rosenberg-Patterson criteria, but three cases (4.7%) were
337 compatible with probable ABPM based on ISHAM criteria and the new diagnostic
338 criteria (Table 4).

339 Among the cases with severe asthma sensitized with *A. fumigatus* that did not fulfill
340 Rosenberg-Patterson criteria of ABPA (n = 26), 14 cases (53.8%) presented with serum
341 IgE levels greater than 1,000 IU/mL, and six patients (23.1%) fulfilled ISHAM criteria.
342 One case (3.8%) with high attenuation mucus on thoracic CT was compatible with
343 definite ABPA, according to the new criteria, and another three cases (11.5%) were
344 diagnosed with probable ABPM (Table 4).

345 Seven cases (29.2%) fulfilled ISHAM criteria among the patients with chronic pulmonary
346 aspergillosis (n = 24), but only one case also exhibited asthma, which is a predisposing
347 condition for the criteria. One case (4.2%) was compatible with probable ABPM in the
348 new criteria, and no case fulfilled the Rosenberg-Patterson criteria (Table 4). Mucus
349 plugs were not microscopically examined in any of the severe asthma or chronic
350 pulmonary aspergillosis cases.

351

352

353 *ROC curve analysis*

354 Sensitivity and specificity for ABPM diagnosis were examined using data from cases
355 with pathological ABPM (n = 79), fungus-negative mucus plugs (n = 37), chronic
356 eosinophilic pneumonia (n = 64), severe asthma with *Aspergillus* sensitization (n = 26),
357 and chronic pulmonary aspergillosis (n = 24).

358 The AUC of ROC curve was 0.85, 0.90, and 0.98 for modified Rosenberg-Patterson
359 criteria (with or without central bronchiectasis), ISHAM criteria, and the new criteria
360 (Figure 2A), respectively. The Youden index was largest for the new diagnostic criteria
361 (0.84 or 0.86) when the cut off value was 5 or 6, which is compatible with the definitions
362 of probable and definite ABPM. The sensitivities for probable/definite and definite ABPM
363 were 96.2% and 89.9%, respectively. The specificities for probable/definite and definite
364 ABPM were 87.4% and 96.0%, respectively.

365 We also validated the new diagnostic criteria excluding component #7 (positive fungal
366 hyphae in mucus plugs), which requires pathological examination. AUC for the new
367 diagnostic criteria was 0.95 in this analysis. The Youden index was largest when the
368 cutoff value was 5, which was compatible with the definition of probable ABPM with the
369 sensitivity and specificity of 90.0% and 91.4%, respectively.

370

371 *Subgroup analyses*

372 Data of 79 cases with pathological ABPM and 179 patients with physician-diagnosed
373 disease were merged for subgroup analyses. A total of 56 ABPM cases had no asthma
374 history (Table E4 in the Online Repository). These patients could not be diagnosed as
375 ABPM using Rosenberg-Patterson criteria because the presence of asthma is
376 mandatory for the criteria. Sensitivity for the diagnosis of ABPM without asthma was
377 relatively high for ISHAM criteria (76.8%) and the new criteria (85.7%, definite/probable
378 ABPM) (Figure 3A).

379 Fungal culture was positive in 130 cases. A total of 108 cases were positive for
380 *Aspergillus spp.*, and 21 cases were positive for non-*Aspergillus* fungi only (Table E5 in
381 the Online Repository). Sensitivity was modest in cases culture-positive for *Aspergillus*
382 *spp.* with Rosenberg-Patterson criteria (42.2%) but was higher with ISHAM criteria
383 (89.9%), and highest with the new criteria (100%) (Figure 3B). In contrast, sensitivity for
384 the cases culture-positive for non-*Aspergillus* fungi alone decreased to 14.3% with

385 Rosenberg-Patterson criteria and 47.6% with ISHAM criteria but remained high for the
386 new criteria (90.5%, Figure 3B).
387

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388 Discussion

389 We validated traditional and new ABPA/ABPM diagnostic criteria by examining cases
390 with pathological ABPM and physician-diagnosed ABPM. The classic diagnostic criteria
391 for ABPA proposed by Rosenberg et al. (1977)⁵ were highly specific with low sensitivity,
392 as previously reported⁹. We are the first to validate the criteria proposed by ISHAM²,
393 showing that the criteria presented substantially improve sensitivity, with a modest
394 decrease in specificity. However, the sensitivity was poor for cases with non-*Aspergillus*
395 ABPM, due to the absence of appropriate serum tests for pathogens excluding
396 *Aspergillus spp.* Therefore, we proposed and validated new diagnostic criteria that
397 showed improved sensitivity and specificity compared to the previous criteria, even in
398 atypical cases without asthma or non-*Aspergillus* ABPM.

399 A major strength of this study is the number and quality of cases with pathologically
400 diagnosed ABPM identified through collaboration between experienced physicians,
401 bronchoscopists, and pathologists. Although resected lungs with ABPA demonstrate
402 various pathological features including mucoid impaction of bronchi, bronchocentric
403 granulomatosis, exudative bronchiolitis, eosinophilic pneumonia, and non-invasive
404 fungal hyphae¹⁴, it is not practical to perform surgical biopsies for the diagnosis of
405 ABPM. Therefore, pathologists proposed that “the finding of mucoid impaction of
406 bronchi containing allergic mucin should suggest the diagnosis of ABPA; if fungal
407 hyphae are present, it is diagnostic”¹⁴. The pathological diagnosis based on the
408 presence of fungal hyphae in allergic mucin, which is an eosinophil-rich mucin in the
409 airways, has also been widely accepted for the diagnosis of allergic fungal rhinosinusitis,
410 an allergic disease associated with fungal colonization in the upper airways¹⁷. In
411 contrast to allergic fungal rhinosinusitis criteria, pathological criteria for ABPM diagnosis
412 have not been popular in clinical practice, due to the requirement of bronchoscopy
413 examinations to obtain appropriate lower airway samples. Instead, immunological tests
414 like *Aspergillus*-specific IgE, IgG, and precipitin have been widely used to diagnose
415 ABPA. Therefore, the limited availability of appropriate serum tests for non-*Aspergillus*
416 fungi has complicated non-*Aspergillus* ABPM diagnosis.

417 Rosenberg-Patterson criteria were highly specific for ABPM but with low sensitivity,
418 especially for cases with pathological ABPM, partly due to the absence of asthma in
419 42% of these cases. Even in cases with asthma, the sensitivities were 40% and 56%
420 with Rosenberg-Patterson criteria for pathological and physician-diagnosed ABPM,

421 respectively. These results are consistent with the previous report by Agarwal et al. who
422 examined the sensitivity of these criteria in 372 asthmatic patients without previous
423 ABPA diagnosis.⁹ Using modified Rosenberg-Patterson criteria with an addition of
424 elevated serum *A. fumigatus*-specific IgE, only 12.5% of the 56 cases with possible
425 ABPA checked all eight components.⁹

426 This is the first study to validate ISHAM criteria for ABPA/ABPM diagnosis. Sensitivities
427 of 77.2% for pathological ABPM and 82.7% for physician-diagnosed disease were
428 significantly better than Rosenberg-Patterson criteria, but with slightly lower specificity,
429 especially for cases with severe asthma with *Aspergillus* sensitization. ISHAM criteria
430 emphasize that high total IgE serum levels ($\geq 1,000$ IU/mL) are essential for
431 differentiating ABPM from asthma with fungal sensitization. However, 23% of the
432 patients with severe asthma with *Aspergillus* sensitization showed IgE levels of 1,000
433 IU/mL or higher in the present study. As did 36% of the cases with severe asthma with
434 fungal sensitization in our previous study.¹⁸ Furthermore, a substantial proportion of
435 patients with ABPA present with IgE levels less than 1,000 IU/mL in our nation-wide
436 survey in Japan¹⁰, and in other studies from East Asia.^{19, 20} High levels of total serum
437 IgE alone are not specific enough for differential diagnosis between ABPM and severe
438 asthma with fungal sensitization. Another pitfall for diagnosis with ISHAM criteria is the
439 handling of predisposing conditions like asthma and cystic fibrosis. If the predisposing
440 conditions are mandatory for ABPM diagnosis, a substantial proportion of patients with
441 pathological and physician-diagnosed ABPM could not have been accurately diagnosed.
442 On the other hand, the ability to differentiate ABPM from chronic pulmonary
443 aspergillosis with ISHAM criteria could be compromised if the presence of asthma is
444 excluded. The third problem for ISHAM criteria is the reduced sensitivity in cases with
445 non-*Aspergillus* ABPM.

446 We developed new diagnostic criteria that emphasize the presence of fungi in the
447 mucus (components #6 and #7), and the importance of mucus plugs in the bronchi
448 (components #9 and #10). Although there is controversy regarding the necessity of
449 separating ABPA/ABPM from severe asthma with fungal sensitization¹², ABPA with
450 intrabronchial mucus plugs that cause central bronchiectasis by expanding inflamed
451 bronchial wall is significantly different pathophysiologically and should be distinguished
452 from fungus-sensitized asthma. Our new criteria showed better sensitivity than previous
453 criteria for diagnosing pathological and physician-diagnosed ABPA/ABPM, with

454 reasonable specificity. Even in the absence of pathological examinations of mucus
455 plugs (component #7), the new criteria still showed improved AUC for ROC curve
456 analysis compared to previous criteria. These results were further confirmed in cases
457 with physician-diagnosed ABPM where pathological examination of mucus plugs was
458 not performed. Therefore, it is practical to apply components #1 - #6 and #8 - #10 of the
459 new diagnostic criteria for ABPM screening. A total score of 6 or more establishes a
460 definite diagnosis without further examination. A bronchoscopy examination to harvest
461 mucus plugs, with a detailed microscopic analysis, would be suggested to confirm the
462 diagnosis for a score of 5.

463 Our study has some limitations. First, our study included only Japanese cases. There
464 are some differences in the ABPA/ABPM disease phenotypes between East- and South
465 Asian populations.³ Furthermore, there are few patients with cystic fibrosis in Japan and
466 the new criteria had not been validated for ABPM predisposed with this condition.
467 Therefore, an international study to validate the new diagnostic criteria is necessary.
468 Second, we employed tentative cut-off values for laboratory tests, like peripheral blood
469 eosinophil counts, total and fungus-specific IgE, IgG, and precipitins, based on the
470 previous diagnostic criteria. However, there are substantial discrepancies between the
471 measurement and interpretation of these parameters, like *Aspergillus*-specific IgG and
472 precipitins, as previously demonstrated.²¹ Further studies are required to determine
473 appropriate cut-off values, especially for patients with different regional/ethnic
474 backgrounds. Third, serum tests for this study were mostly performed using crude
475 fungal extracts, and the presence of cross-reactivity among different fungi could have
476 compromised ABPM diagnosis. Molecular allergy diagnostics based on allergenic
477 component-specific serum tests may be a promising way to improve the accuracy of
478 ABPA/ABPM diagnosis.²⁰

479 In conclusion, the new ten-component diagnostic criteria would be useful in diagnosing
480 ABPA/ABPM with improved sensitivity and specificity.

481

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553

554 **Figure legends**

555

556 **Figure 1. Sensitivity of diagnostic criteria for pathological and**
557 **physician-diagnosed ABPM**

558 Sensitivity for pathological ABPM (A, n = 79) and physician-diagnosed ABPM (B, n =
559 179) were compared between the Rosenberg-Patterson criteria, ISHAM criteria, and the
560 new diagnostic criteria. Red bars represent definite ABPM. Blue bars show probable
561 cases.

562

563 **Figure 2. ROC curve analysis for the diagnosis of pathological ABPM**

564 ROC curve analysis for differential diagnosis between pathological ABPM (n = 79) and
565 control diseases (fungus-negative mucus plugs, chronic eosinophilic pneumonia,
566 severe asthma with *Aspergillus* sensitization, and chronic pulmonary aspergillosis, n =
567 151) with Rosenberg-Patterson criteria (violet line), ISHAM criteria (blue line), and new
568 criteria (red line). The red dotted line represents the result with new diagnostic criteria
569 excluding component #7 (positive fungal hyphae in mucus plugs), which requires
570 pathological examination.

571

572 **Figure 3. Sensitivity of diagnostic criteria for ABPM with/without asthma and**
573 ***Aspergillus*/non-*Aspergillus* ABPM**

574 Sensitivity for (A) ABPM with asthma (n = 202) and without asthma (n = 56), (B)
575 culture-positive ABPA (n = 108) and non-*Aspergillus* ABPM (n = 21), were compared
576 using Rosenberg-Patterson criteria, ISHAM's criteria, and the new diagnostic criteria.
577 Red bars represent definite ABPM, and blue bars indicate probable cases.

578

579

580

581 **Table 1. Clinical diagnostic criteria for allergic bronchopulmonary mycosis in**
582 **patients without cystic fibrosis**

584	1.	Current or previous history of asthma or asthmatic symptoms
585	2.	Peripheral blood eosinophilia (≥ 500 cells/mm ³)
586	3.	Elevated total serum immunoglobulin E levels (IgE ≥ 417 IU/mL)
587	4.	Immediate cutaneous hypersensitivity or specific IgE for filamentous fungi
588	5.	Presence of precipitins or specific IgG for filamentous fungi
589	6.	Filamentous fungal growth in sputum cultures or bronchial lavage fluid
590	7.	Presence of fungal hyphae in bronchial mucus plugs
591	8.	Central bronchiectasis on computed tomography (CT)
592	9.	Presence of mucus plugs in central bronchi, based on CT/bronchoscopy or
593		mucus plug expectoration history
594	10.	High attenuation mucus in the bronchi on CT

595

596 Filamentous fungi in 4-6 should be identical.

597 Patients that meet 6 or more of these criteria are diagnosed with ABPM.

598

599 **Table 2. Demographic and laboratory data of patients with ABPM**

	Pathological ABPM	Physician-diagnosed ABPM	P value
Number of subjects	79	179	
Age, years	59±15	61±14	n.s.
Female, n (%)	49 (62)	98 (55)	n.s.
Asthma, n (%)	46 (58)	156 (87)	< 0.001
Peripheral blood eosinophil counts, / μ L	900 (574-1,700)	1,280 (720-2,214)	< 0.001
Serum IgE levels, IU/mL	1,983 (515-5,600)	2,240 (1,033-5,950)	n.s.
Fungus-specific hypersensitivity			
Fungus-specific IgE or immediate cutaneous reactions, n (%)	75 (95)	171 (96)	n.s.
Fungus-specific precipitin, IgG, or Arthus-type cutaneous reactions, n (%)	46 (61) ^a	137 (77)	n.s.
Fungal culture in sputum or bronchial samples, n (%)	50 (64) ^b	81 (74) ^c	n.s.
<i>Aspergillus</i> spp., n (%)	40 (51) ^b	68 (62) ^c	n.s.
<i>A. fumigatus</i> , n (%)	35 (44)	38 (35)	
<i>Aspergillus</i> sp. other than <i>A. fumigatus</i> , n (%)	5 (6)	13 (12)	
<i>Aspergillus</i> sp., unclassifiable, n (%)	0 (0)	17 (16)	
Other filamentous fungi, n (%)	10 (13) ^b	13 (12) ^c	n.s.
<i>Schizophyllum commune</i> , n (%)	6 (8)	4 (4)	
<i>Penicillium</i> spp., n (%)	2 (3)	2 (2)	
Others or unclassifiable, n (%)	2 (3)	7 (6)	
Fungal hyphae in mucus plugs, n (%)	79 (100)	N/A	-
Thoracic computed tomography			
Lung opacities, n (%)	78 (99)	159 (89)	< 0.001
Central bronchiectasis, n (%)	46 (58)	148 (83)	< 0.001
Mucus plugs in bronchi, n (%)	58 (73)	118 (82) ^d	n.s.
High attenuation mucus, n (%)	42 (53)	67 (47) ^d	n.s.

600 ^a n = 76, ^b n = 78, ^c n = 109, ^d n = 144

601 ABPM, allergic bronchopulmonary mycosis; N/A, not analyzed; n.s., not significant

602

603 **Table 3. Demographic and laboratory data of the control population**

	Mucus plugs without fungal hyphae	Chronic eosinophilic pneumonia	Severe asthma with <i>Aspergillus</i> sensitization	Chronic pulmonary aspergillosis
Number of subjects	37	64	26	24
Age, years	54±14	55±12	64±14	65±13
Female, n (%)	18 (49)	44 (69)	11 (42)	4 (17)
Asthma, n (%)	36 (97)	31 (48)	26 (100)	3 (13)
Peripheral blood eosinophil counts, /mL	1,104 (559-2,104)	1,400 (600-2,700)	317 (167-530)	201 (74-713)
Serum IgE levels, IU/mL	326 (170-1,389)	371 (182-943)	1,155 (231-3,035)	107 (36-1,048)
Fungus-specific hypersensitivity				
Fungus-specific IgE or immediate cutaneous reactions, n (%)	8 (22)	11 (17)	26 (100)	13 (54)
Fungus-specific precipitin, IgG, or Arthus-type cutaneous reactions, n (%)	5 (14)	0 (0)	5 (19)	19 (79)
Fungal culture in sputum or bronchial samples, n (%)	0 (0)	0 (0)	5 (33) ^a	12 (52) ^b
<i>Aspergillus</i> spp., n (%)	0 (0)	0 (0)	5 (33)	10 (43)
Other filamentous fungi, n (%)	0 (0)	0 (0)	0 (0)	2 (5)
Fungal hyphae in mucus plugs, n (%)	0 (0)	N/A	N/A	N/A
Thoracic computed tomography				
Lung opacities, n (%)	25 (68)	67 (100)	11 (42)	18 (75)
Central bronchiectasis, n (%)	2 (6)	2 (3)	3 (12)	6 (25)
Mucus plugs in bronchi, n (%)	7 (19)	15 (23)	1 (4)	2 (8)
High attenuation mucus, n (%)	6 (16)	0 (0)	1 (4)	0 (0)

604 ^a n = 15, ^b n = 23

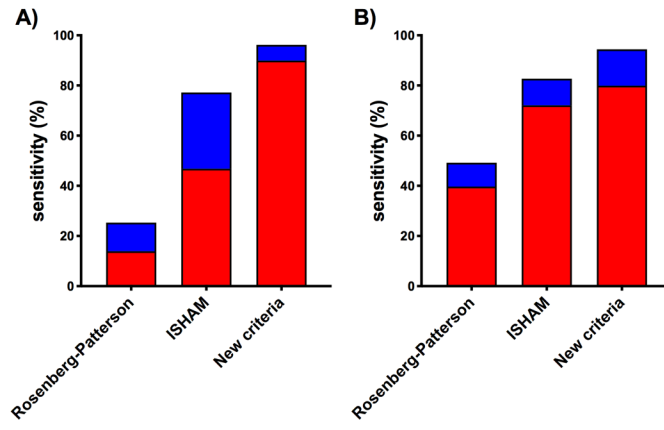
605 N/A, not analyzed

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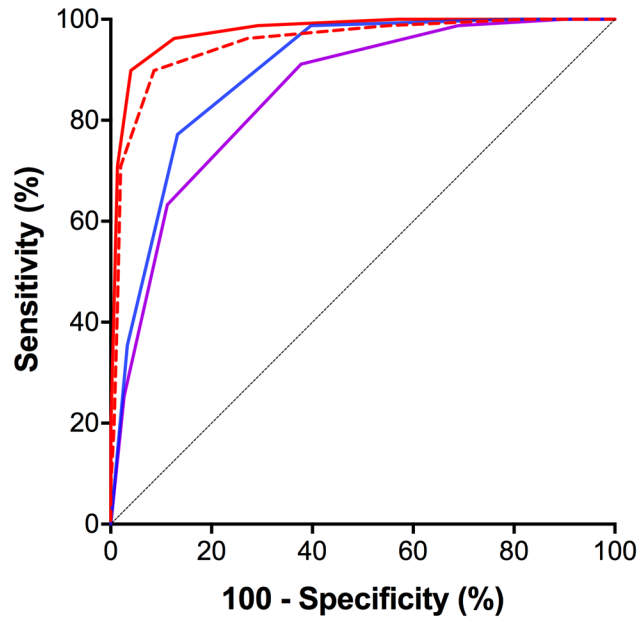
607 **Table 4. Pseudo-positive cases in control diseases**

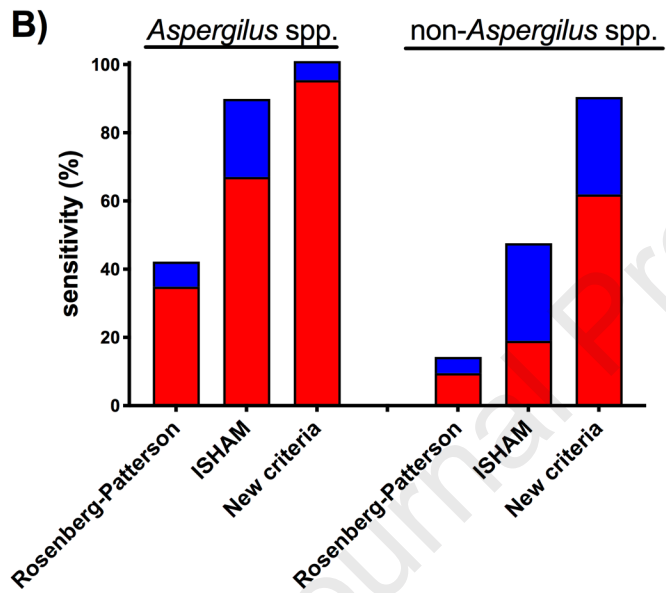
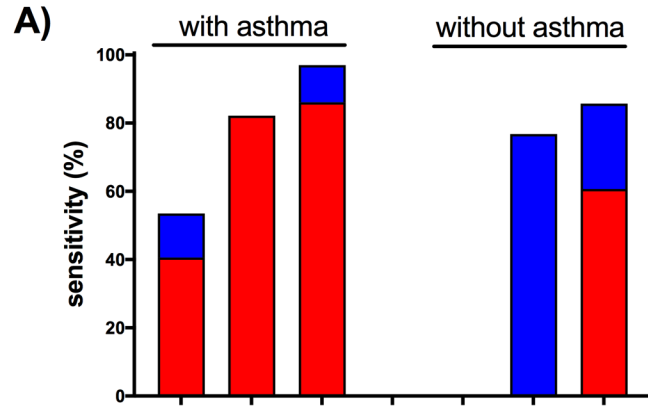
	n	Rosenberg-Paterson		ISHAM		New Criteria	
		definite	definite/probable	definite	definite/probable	definite	definite/probable
Mucus plugs without fungal hyphae, n (%)	37	1 (3)	2 (5)	4 (11)	4 (11)	4 (11)	7 (19)
Chronic eosinophilic pneumonia, n (%)	64	0 (0)	0 (0)	3 (5)	3 (5)	0 (0)	3 (5)
Severe asthma with <i>Aspergillus</i> sensitization, n (%)	26	N/A	N/A	6 (23)	6 (23)	1 (4)	4 (15)
Chronic pulmonary aspergillosis, n (%)	24	0 (0)	0 (0)	1 (4)	7 (29)	0 (0)	1 (4)

608 N/A, not analyzed



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New Clinical Diagnostic Criteria for Allergic Bronchopulmonary
Aspergillosis/Mycosis and its Validation

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Table E1. Modified Rosenberg-Patterson diagnostic criteria

-
1. Episodic bronchial obstruction (asthma)
 2. Peripheral blood eosinophilia ($\geq 500/\text{mm}^3$)
 3. Immediate skin reactivity or specific IgE antibody to filamentous fungal antigen
 4. Precipitating antibodies or IgG antibodies against filamentous fungal antigen
 5. Elevated serum IgE concentrations ($\geq 417 \text{ IU/mL}$)
 6. History of pulmonary infiltrates (transient or fixed)
 7. Central bronchiectasis
-

Cases that checked all seven components were considered definite ABPM. Cases fulfilling six components, except for central bronchiectasis (#7), were designated as probable cases.

Table E2. Modified ISHAM diagnostic criteria

Predisposing conditions

asthma, cystic fibrosis

Obligatory criteria (both should be present)

1. Immediate cutaneous hypersensitivity or elevated IgE levels against filamentous fungi
2. Elevated serum IgE concentrations ($\geq 1,000$ IU/mL)

Other criteria (at least two)

1. Precipitating antibodies or IgG antibodies against filamentous fungal antigen
 2. Radiographic pulmonary opacities consistent with ABPA*
 3. Peripheral blood eosinophilia ($\geq 500/\text{mm}^3$)
-

*The chest radiographic features consistent with ABPA may be transient (i.e., consolidation, nodules, tram-track opacities, toothpaste/finger-in-glove opacities, or fleeting opacities) or permanent (i.e., parallel line and ring shadows, bronchiectasis, or pleuropulmonary fibrosis).

An IgE value $< 1,000$ IU/mL may be acceptable if the patient met all other criteria.

A case without any predisposing conditions was probable ABPM.

Table E3. Comparison of demographic data for pathological ABPM between institutes

	Institute A n = 54	Institute B n = 25	P value
Age, years	59±15	59±15	n.s.
Female, n (%)	33 (61)	16 (64)	n.s.
History of asthma, n (%)	35 (64)	11 (44)	n.s.
Peripheral blood eosinophil counts	967 (602-1,764)	900 (450-1,600)	n.s.
Total serum IgE levels	1,707 (447-4,961)	2,007 (855-6,476)	n.s.
Fungus-specific hypersensitivity			
Fungus-specific IgE or immediate cutaneous reactions, n (%)	53 (98)	22 (88)	n.s.
Fungus-specific precipitin, IgG, or Arthus-type cutaneous reactions, n (%)	33 (61)	13 (52)	n.s.
Fungal culture, n (%)	30 (57) [n=53]	20 (80)	n.s.
<i>Aspergillus</i> spp., n (%)	28 (53)	12 (48)	n.s.
Other filamentous fungi, n (%)	2 (4)	8 (32)	0.001
Thoracic computed tomography			
Lung opacities, n (%)	53 (98)	25 (100)	n.s.
Central bronchiectasis, n (%)	21 (39)	25 (100)	<0.001
Mucus plugs in bronchi, n (%)	34 (63)	24 (96)	0.001
High attenuation mucus, n (%)	28 (52)	14 (56)	n.s.

n.s., not significant

Table E4. Comparisons of demographic data for ABPM with or without asthma

	With asthma n = 202	Without asthma n = 56	P value
Age, years	59±14	65±13	0.005
Female, n (%)	114 (57)	35 (63)	n.s.
Peripheral blood eosinophil counts	1210 (700-2,204)	1086 (594-1,508)	n.s.
Total serum IgE levels	2,439 (1,034-6,111)	1,499 (520-3,933)	n.s.
Fungus-specific hypersensitivity			
Fungus-specific IgE or immediate cutaneous reactions, n (%)	191 (95)	54 (96)	n.s.
Fungus-specific precipitin, IgG, or Arthus-type cutaneous reactions, n (%)	146 (72)	34 (61)	n.s.
Fungal culture, n (%)	94 (67) [n=140]	38 (80) [n=48]	n.s.
<i>Aspergillus</i> spp., n (%)	83 (59)	25 (48)	0.005
Other filamentous fungi, n (%)	11 (8)	13 (32)	
Thoracic computed tomography			
Lung opacities, n (%)	182 (90)	55 (98)	n.s.
Central bronchiectasis, n (%)	157 (78)	37 (66)	<0.001
Mucus plugs in bronchi, n (%)	130 (78) [n=167]	46 (82)	0.001
High attenuation mucus, n (%)	83 (50) [n=166]	25 (45)	n.s.

n.s., not significant

Table E5. Comparisons of demographic data between culture-positive ABPA and non-*Aspergillus* ABPM

	Culture-positive ABPA n = 108	non- <i>Aspergillus</i> ABPM n = 21	P value
Age, years	62±15	59±9	n.s.
Female, n (%)	66 (62)	15 (71)	n.s.
History of asthma, n (%)	83 (77)	8 (38)	0.001
Peripheral blood eosinophil counts	1,344 (710-2,206)	780 (500-1,300)	0.006
Total serum IgE levels	2,305 (1,095-6,538)	1,391 (461-3,755)	n.s.
Fungus-specific hypersensitivity			
Fungus-specific IgE or immediate cutaneous reactions, n (%)	106 (98)	20 (95)	n.s.
Fungus-specific precipitin, IgG, or Arthus-type cutaneous reactions, n (%)	87 (81)	7 (33)	<0.001
Thoracic computed tomography			
Lung opacities, n (%)	101 (94)	18 (86)	n.s.
Central bronchiectasis, n (%)	83 (77)	16 (76)	n.s.
Mucus plugs in bronchi, n (%)	72 (78) [n=92]	19 (95) [n=20]	n.s.
High attenuation mucus, n (%)	46 (50) [n=92]	14 (70) [n=20]	n.s.

n.s., not significant