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11 **Epidemiology and outcomes of allergic bronchopulmonary aspergillosis** 12 **in the elderly**

13 (Running title: ABPA in elderly)

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49 **ABSTRACT**

50 **BACKGROUND:** The prevalence and outcomes of allergic bronchopulmonary aspergillosis (ABPA)
51 in the elderly remain unknown.

52 **METHODS:** We reviewed our database to identify the proportion of subjects diagnosed with
53 ABPA at ≥ 60 years of age (ABPA-elderly). We compared the clinical features, treatment, and
54 outcomes of ABPA-elderly versus the non-elderly (ABPA diagnosed at < 60 years of age).

55 **RESULTS:** Between 2007 and 2019, we encountered 810 ABPA subjects with a mean age of 34.9
56 years (49.4% women). Of these, 43 (5.3%) were aged ≥ 60 years (ABPA-elderly). There was a trend
57 towards lower median (interquartile range [IQR]) serum total IgE (4900 [2659-10000] vs. 7156
58 [23360-11963] IU/mL; $p=0.06$) and *Aspergillus fumigatus*-specific IgE (12.3 [4.8-29.6] vs. 22.4
59 [7.7-41.5] kUA/L; $p=0.06$) in the elderly than the non-elderly. Eosinophil counts were similar in
60 the two groups. The median [IQR] number of segments involved by bronchiectasis (5 [2-9] vs. 7
61 [4-11]) was significantly lower in the ABPA-elderly ($p=0.001$). The proportion of subjects
62 experiencing ABPA exacerbations was significantly ($p=0.047$) lower in the elderly (25.6%) vs. the
63 non-elderly (40.8%). There was also a tendency towards a lower mean number of exacerbations
64 in the elderly (155 vs. 208 exacerbation per 1000 person-years) than the non-elderly ($p=0.09$).
65 There was also a trend towards longer mean time to first exacerbation in the ABPA-elderly than
66 the non-elderly (1612 vs. 1159 days).

67 **CONCLUSION:** ABPA was uncommon in the elderly. The bronchiectasis is less extensive with a
68 trend towards lower immunological severity and fewer exacerbations in the elderly than the non-
69 elderly subjects with ABPA.

70 **Keywords:** aspergillosis; ABPM; asthma; allergy; bronchiectasis; *Aspergillus*

71 INTRODUCTION

72 Allergic bronchopulmonary aspergillosis (ABPA) is a pulmonary allergy caused by immune
73 responses targeted against *Aspergillus fumigatus* colonizing the airways of asthma (and cystic
74 fibrosis) patients.¹ Patients with ABPA commonly present with difficult-to-treat asthma,
75 recurrent pulmonary opacities, and bronchiectasis.² The clinical course of ABPA is punctuated by
76 recurrent exacerbations.³ The prevalence of ABPA in adult asthmatics ranges from 2-3.5% in
77 secondary care cohorts.⁴ The global burden of the disease is estimated at 5 million cases, with
78 1.4 million cases in India alone.⁵

79 ABPA is a disease of young and middle-aged adults.⁶ However, in certain parts of the
80 world (especially Japan and Korea), ABPA has been reported mainly in the elderly.⁷⁻¹² The natural
81 history and course of ABPA in the elderly, however, remains unclear. The adaptive immune
82 responses start waning with increasing age. We hypothesized that ABPA might be associated
83 with less intense immune responses in the elderly. In this study, we report the prevalence of
84 elderly ABPA in an outpatient hospital cohort. We also compare the immunological and imaging
85 findings and the exacerbation frequency in the elderly versus the non-elderly subjects with ABPA.

86 METHODS

87 We retrospectively reviewed our clinic database to identify subjects with ABPA over the
 88 last 13 years (1st January 2007 to 31st December 2019). The Institutional ethics committee
 89 approved the study protocol, and a consent waiver was granted as we used anonymized patient
 90 data. A part of the data has been published previously.¹³⁻¹⁷
 91 Inclusion and exclusion criteria: We included treatment-naïve cases of ABPA diagnosed according
 92 to the ISHAM-ABPA working group criteria, with certain modifications.¹⁸⁻²¹ Briefly, the patient
 93 should have met five or more of the following criteria: (1) physician-diagnosed asthma; (2) raised
 94 *A.fumigatus*-specific IgE (>0.35 kUA/L) or immediate cutaneous hypersensitivity demonstrated by
 95 *Aspergillus* skin test; (3) elevated serum total IgE >500 IU/mL; (4) serum precipitating antibodies
 96 against *A.fumigatus* or *A.fumigatus* specific IgG ≥27 mgA/L; (5) peripheral blood eosinophilia
 97 >500 cells/μL; (6) fleeting opacities and finger-in-glove opacities on the chest radiograph; (7)
 98 computed tomography (CT) of the chest showing bronchiectasis or high attenuation mucus
 99 (HAM). We excluded subjects with any of the following: (1) intake of systemic glucocorticoids or
 100 triazoles for >3 weeks in the past; and (2) inadequate details.

101 Study objectives: Our objectives were to: (1) ascertain the proportion of subjects aged ≥60 years
 102 at the time of diagnosing ABPA; and (2) compare the demography, clinical features,
 103 immunological investigations, treatment, and follow-up of ABPA in the 'elderly' versus 'non-
 104 elderly'. We classified the elderly as age ≥60 years according to the Central Statistics Office of
 105 India definition.²² Further, as an exploratory analysis, we compared the immunological
 106 parameters (serum total IgE, total eosinophil count, *A.fumigatus*-specific-IgE, and -IgG) in three
 107 arbitrarily defined age groups (≤45, 46-59, and ≥60 years).

108 Study procedure: We extracted the following information from our records: (1) history and
 109 duration of asthma; (2) history of anti-tuberculosis therapy in the past; (3) details of
 110 immunological investigations and imaging data; (4) treatment received; (5) frequency of
 111 exacerbations; and (6) duration of follow-up.

112 We used the commercially available fluorescent enzyme immunoassay (Phadia 100,
 113 Thermo Fisher Scientific, Uppsala, Sweden) to measure the serum total IgE and *A.fumigatus*-
 114 specific IgE and IgG.²³⁻²⁵ Serum *Aspergillus* precipitins were measured using the double-gel
 115 diffusion technique. We used a 16-row, multiple-detector scanner (LightSpeed plus, GE medical

116 systems, Slough UK) for performing CT of the chest. We recorded the extent of bronchiectasis
 117 and the presence of high-attenuation mucus (HAM).^{26,27} We performed spirometry at baseline
 118 and graded the severity of obstruction as mild, moderate, or severe.²⁸

119 We treated the subjects with either oral glucocorticoids or antifungal triazoles for four
 120 months, as described previously, for treating ABPA.^{14,16,17,29} We monitored the patient every 6-8
 121 weeks with a chest radiograph and serum total IgE. Response was defined as clinical and
 122 radiological resolution and a decline in serum total IgE by at least 25% of the baseline value. We
 123 diagnosed ABPA exacerbation if the serum total IgE increased by >50% from the last recorded
 124 IgE, with clinical or radiologic worsening. We managed the first exacerbation of ABPA with oral
 125 prednisolone and subsequent exacerbations with a combination of prednisolone and antifungal
 126 triazole.³⁰ Clinical worsening of symptoms in the absence of radiological or immunological (serum
 127 total IgE) worsening was labeled as asthma exacerbation and managed accordingly. We defined
 128 frequent asthma or ABPA exacerbations as the occurrence of two or more exacerbations during
 129 the patient follow-up.¹⁵ Inhaled corticosteroids, long- and short-acting beta-2 agonists, and
 130 montelukast were used for asthma control at the treating physician's discretion.

131 Statistical analysis: We analyzed the data using the commercial statistical package SPSS for MS-
 132 Windows (version 22.0, IBM Inc., Armonk, NY). Categorical variables were expressed as numbers
 133 and percentages. Continuous variables were expressed as mean (95% confidence intervals [CI])
 134 or median with interquartile range (IQR), as applicable. We compared the categorical variables
 135 using the Chi-square test, while the student's t-test (or the Mann-Whitney U test) was used for
 136 continuous variables. We compared the immunological parameters (serum total IgE, total
 137 eosinophil count, *A.fumigatus* specific-IgE, and -IgG) between the study groups (≤ 45 , 46-59, and
 138 ≥ 60 years) using the Kruskal-Wallis analysis of variance and presented the data as a violin plot.
 139 We used the Bonferroni correction to adjust the significance values for multiple comparisons.
 140 Additionally, we calculated the incidence rate of ABPA exacerbation per 1000 patient-years (PY;
 141 the sum of the number of exacerbations in each subject/sum of the number of years each
 142 subject was followed up, multiplied by 1000) and compared it between the two study groups.
 143 We also calculated the time to first exacerbation in the ABPA-elderly and the non-elderly using
 144 Kaplan-Meier survival analysis. The differences between the two groups were analyzed using the
 145 log-rank test. A p-value <0.05 was considered statistically significant.

RESULTS

We included 810 participants with ABPA in the current study (Table 1). The study subjects met the diagnosis of ABPA by one or more of the Patterson (n=636), ISHAM (n=534), and the modified ISHAM (n=677) criteria. The study population's mean (95% CI) age was 34.9 (34-35.8) years, and the age distribution is shown in Figure 1. We identified 43 elderly (mean [range] age, 65 [60-80] years) and 767 non-elderly (mean [range] age 33.2 [12-59] years) subjects. The proportion (95% CI) of elderly among the ABPA subjects was 5.3% (95% CI, 3.9-7.1).

Baseline characteristics: We did not find a statistically significant difference in the sex distribution, smoking status, clinical features, and anthropometry in the ABPA-elderly versus the non-elderly (Table 1). However, the duration of asthma was significantly longer, and a previous history of antitubercular therapy was less frequent in the elderly than the non-elderly. The age of onset of asthma was significantly different between the two groups (Figure 2). The childhood-onset (<13 years) of asthma was more frequent in the non-elderly ABPA than in the elderly (24.4% vs. 2.3%, $p=0.0001$). Elderly participants had significantly lesser FEV1 and FVC than the non-elderly. However, the predicted FEV1 and FVC for the age, the proportion of subjects with abnormal spirometry, and the various severity grades did not differ between the two study groups (Table 1).

Immunological tests: The median serum IgE (both total and *A. fumigatus*-specific) showed a propensity ($p=0.06$) towards lower values in the elderly than the non-elderly subjects (Table 1). The total eosinophil count and *A. fumigatus*-specific IgG were similar in the two groups.

Additionally, we compared *A. fumigatus* specific-IgE, serum total IgE, *A. fumigatus*-specific IgG, and total eosinophil count across three age groups (Figure 3). The distribution of serum total IgE ($p=0.03$) and *A. fumigatus*-specific IgE levels ($p=0.022$) differed significantly between the three groups. However, when adjusted for multiple comparisons, only the *A. fumigatus*-specific IgE was significantly lower in the ≥ 60 years subgroup than 46-59 years (Figure 3). There was no statistically significant difference in total eosinophil count ($p=0.26$) and *A. fumigatus*-specific IgG ($p=0.92$) among the three groups.

Imaging: The median (IQR) number of lobes and segments affected by bronchiectasis was 4 (2-5) and 7 (4-11), respectively. The severity of bronchiectasis on imaging was significantly lesser in the

175 elderly (Table 1). We found HAM in 35.3% of subjects, and the proportion was lower in the
176 elderly than the non-elderly subjects (Table 1).

177 Follow-up: We followed up the subjects for a mean duration of 63.3 months (Table 2). The
178 proportion of subjects treated with glucocorticoids or antifungal triazoles was not statistically
179 different between the study groups. Asthma exacerbation was seen in 41.8% of subjects (Table
180 2). We did not find a statistically significant difference in the proportion of participants
181 experiencing asthma exacerbation, frequent asthma exacerbations (≥ 2) or the mean number of
182 asthma exacerbations per 1000 PY follow-up. ABPA exacerbation occurred in 324/810 (40%)
183 subjects. A lower proportion of elderly subjects experienced an ABPA exacerbation than the non-
184 elderly (25.6% vs. 40.8%; $p=0.047$). There was also a bearing towards a lower mean number of
185 ABPA exacerbations during follow-up (155 vs. 208 per 1000 PY for the elderly and non-elderly,
186 respectively), albeit not statistically significant ($p=0.09$). The information on the time to first
187 exacerbation was available in 463 subjects. Of these, 6/26 and 196/437 of the ABPA-elderly and
188 the non-elderly, respectively, developed exacerbation (Figure 4). The mean (95% CI) time to the
189 first exacerbation was 1159 (1073-1245) vs. 1612 (1263-1960) days in the non-elderly vs. the
190 elderly, respectively ($p=0.06$).

DISCUSSION

In a large dataset over a 13-year study period, we found elderly ABPA in only 5.3% of the total ABPA cases. Further, ABPA in the elderly was characterized by less severe bronchiectasis on imaging and a trend towards lower serum total IgE and *A.fumigatus*-specific IgE than the non-elderly. While there was no difference in the asthma exacerbation rates between the elderly and non-elderly, there was a tendency towards lower ABPA exacerbations in the elderly.

The human immune system undergoes considerable age-related changes, generally beginning with the sixth decade of life.³¹ Aging affects the immune system at different levels, including decreased B and T lymphocytes production in the bone marrow. Consequently, there is decreased immune response against infections, cancer, and vaccines.³² Moreover, the production of serum total and antigen-specific IgE declines with increasing age.³³⁻³⁵ Even in the current study, the IgE values were lower in the elderly subgroup. We also performed an exploratory analysis to ascertain whether the IgE values varied by age subgroups (≤ 45 , 46-59, ≥ 60 years). However, we did not find any difference in the lower age categories (≤ 45 vs. 46-59 years). The underlying airway inflammation in elderly asthmatic patients differs from the young asthma patients and is more likely to be predominated by pathways other than type 2.³⁶ Asthma in the elderly is associated with higher morbidity than the younger population.³⁷ Contrarily, we found no significant difference in the proportion of ABPA patients with asthma exacerbations, frequent asthma exacerbations, and the number of asthma exacerbations per 1000 person-years, possibly due to the better treatment of the underlying ABPA.

In a large study of 1,258 patients with non-cystic fibrosis bronchiectasis, ABPA was the etiology in only 3.3%,³⁸ and it was found with a similar frequency in the young and the older patients.³⁸ However, several studies published from Japan and Korea suggest that ABPA has an older age of onset.⁷⁻¹² Most of these studies are limited by their small size and have included non-consecutive patients of ABPA.⁷⁻¹¹ In a nationwide dataset of 358 cases from Japan, the authors reported the median age of presentation of ABPA to be 64 years.¹² There was no difference in the imaging findings or exacerbations in patients below or above 50 years. Further in this study, elderly patients had a shorter duration of asthma before ABPA diagnosis than younger patients. In contrast, in the present study, the elderly patients had a longer duration of asthma before diagnosing ABPA than younger patients. Our study also found several differences

221 in the immunological and imaging findings and exacerbations in the elderly. The possible reasons
222 for the difference could be the cut-off used for categorizing the elderly (60 years cut-off in the
223 present study vs. 50 years in the Japanese study) and the study design (ours was a longitudinal
224 study while the Japanese study was cross-sectional). Whether certain unknown environmental or
225 genetic factors influence the development of ABPA in elderly Japanese patients remains
226 speculative.

227 What are the clinical implications of our study? It is of great clinical value to delineate a
228 disease's natural history and course in specific subgroups, including children, pregnancy, the
229 elderly, and others.^{39,40} Our results suggest that elderly patients with ABPA have a less severe
230 immunological and radiological disease and possibly better outcomes than the young. It can be
231 hypothesized that the elderly subgroup could be managed with lesser doses and duration of
232 glucocorticoids or with triazole monotherapy for a shorter duration.

233 Finally, our study is not without limitations. Our study is a single-center study. Due to the
234 retrospective nature and the long study duration, the subjects were diagnosed using different
235 ABPA criteria and received various treatments over the study duration. Further, we do not have
236 the data on asthma exacerbations in all the study subjects. We do not have the specific
237 symptoms in the elderly that led to a diagnosis of ABPA. The duration of follow-up varied
238 between participants and can potentially affect the exacerbation frequency. However, we
239 normalized the duration by using patient-years for reporting the exacerbation frequency and also
240 noted the time to first exacerbation. Also, we have not systematically evaluated the patients for
241 any underlying mutations predisposing them to ABPA. Finally, we noted clinically significant
242 differences in certain parameters between elderly and non-elderly subjects with ABPA; a larger
243 sample size of the elderly subjects might have identified a statistically significant difference.

244 In conclusion, we found that ABPA is uncommon in the elderly. Moreover, the disease is
245 less severe immunologically and radiologically, with lower exacerbations in the elderly than the
246 non-elderly subjects with ABPA.

247 Table 1: Baseline clinical features, immunological investigations, spirometry, and imaging findings of ABPA
 248 patients

Parameter	ABPA in elderly (n=43)	ABPA non-elderly (n=767)	P-value
Clinical features			
^a Age, years	65 (63.2-66.7)	33.2 (32.4-34)	0.0001
Male sex	18/43 (41.9)	392/767 (51.1)	0.24
Asthma	37/43 (86)	714/766 (93.2)	0.08
^a Duration of asthma, in years	17.4 (12.2-22.6)	11.6 (10.9-12.2)	0.001
Smokers	1/43 (2.3)	12/767 (1.6)	0.56
Hemoptysis	15/43 (34.9)	243/767 (31.7)	0.66
Expectoration of BBMP	10/43 (23.3)	201/767 (26.2)	0.67
History of ATT intake	7/43 (16.3)	269/767 (35.1)	0.04
^a Height, cm	159.2 (156.3-162.1)	162.5 (161.7-163.3)	0.07
^a Weight, kg	55.9 (51.8-60.0)	55.1 (54.1-56.2)	0.73
Spirometry^a			
FEV1, liters	1.46 (1.26-1.67)	1.92 (1.85-1.99)	0.01
FVC, liters	2.28 (2.07-2.50)	2.74 (2.67-2.82)	0.04
FEV1/FVC	62.4 (58.2-66.5)	67.8 (66.7-68.9)	0.02
FEV1, %pred	66.5 (22.1)	69.9 (21.6)	0.39
FVC, %pred	71.2 (18.6)	83 (15.9)	0.08
FEV1/FVC, %pred	80.1 (15.7)	77.4 (14.8)	0.35
Spirometry category			0.53
Normal	13/42 (31)	206/741 (27.8)	
Mild obstruction	15/42 (35.7)	227/741 (30.6)	
Moderate	11/42 (26.7)	196/741 (26.5)	
Severe	3/42 (7.1)	112/741 (15.1)	
Immunological tests			
^b <i>A.fumigatus</i> specific IgE, kUA/L (n=808)	12.3 (4.8-29.6)	22.4 (7.7-41.5)	0.06
Positive <i>Aspergillus</i> skin test	38/42 (90.5)	705/763 (92.4)	0.87
^b Total IgE, IU/mL (n=810)	4900 (2659-10000)	7156 (3360-11963)	0.06
^b Total eosinophil count, cells/ μ L (n=809)	515 (236-1292)	800 (400-1402)	0.11

^b <i>A.fumigatus</i> specific IgG, mgA/L (n=248)	98 (47.6-134)	87 (48.6-174)	0.87
Positive serum <i>Aspergillus</i> precipitins	22/42 (52.4)	384/762 (50.4)	0.80

Imaging

Fleeting opacities on chest radiograph	13/29 (44.8)	280/531 (52.7)	0.41
Bronchiectasis	35/43 (81.4)	669/759 (88.1)	0.19
^b Number of lobes involved (n=752)	3 (1-4)	4 (2-5)	0.001
^b Number of segments involved (n=802)	5 (2-9)	7 (4-11)	0.005
Presence of HAM	8/43 (18.6)	278/766 (36.3)	0.02

249 %pred – percentage predicted; ABPA – allergic bronchopulmonary aspergillosis; AEC – absolute eosinophil count;
 250 ATT – antitubercular therapy; Asp – *Aspergillus fumigatus*; BBMP – brownish black mucus plug; BDPE –
 251 beclomethasone dipropionate equivalent; ICS – inhaled corticosteroid; FEV1 – forced expiratory volume in one
 252 second; FVC – forced vital capacity; HAM – high-attenuation mucus; IgE – immunoglobulin E; PY – person-years
 253 All values are presented as n/N (percentages), unless otherwise mentioned as ^amean (95% confidence interval) or
 254 ^bmedian (first quartile-third quartile)

255 Table 2: Treatment and follow-up of the ABPA patients included in the study

Parameter	ABPA in elderly (n=43)	ABPA non- elderly (n=767)	P-value
^a Follow-up duration, in months	61.3 (46.6-76)	63.4 (60.1-66.8)	0.77
Treatment details			
^a Dosage of ICS (BDPE), µg	595 (390-800)	539 (494-584)	0.57
Glucocorticoid therapy	24/43 (55.8)	417/767 (54.4)	0.98
Itraconazole therapy	5/43 (11.6)	59/767 (7.7)	0.52
Voriconazole therapy	3/43 (7)	22/767 (2.9)	0.29
Asthma exacerbations (n=414)			
Proportion with asthma exacerbation	5/21 (23.8)	168/393 (42.7)	0.11
Frequent asthma exacerbations (≥2)	4/21 (19.0)	78/393 (19.8)	1.00
^b Number of asthma exacerbations per 1000 PY [¶]	162 (40-365)	117 (98-136)	0.26
ABPA exacerbations			
Proportion with ABPA exacerbation	11/43 (25.6)	313/767 (40.8)	0.047
Frequent ABPA exacerbations (≥2)	7/43 (16.3)	170/767 (22.2)	0.36
^a Number of ABPA exacerbations per 1000 PY [¶]	155 (49-261)	208 (180-238)	0.09

256 All values are presented as n/N (percentages), unless otherwise mentioned as ^amean (95% confidence interval) or257 ^bmedian (first quartile-third quartile)

258 [¶]Number of exacerbations per 1000 person-years = (Sum of the number of exacerbations experienced by each
 259 participant/sum of the number years each participant was followed-up) X 1000. This information was available for
 260 614 subjects

261 ABPA – allergic bronchopulmonary aspergillosis; BDPE – beclomethasone dipropionate equivalent; ICS – inhaled
 262 corticosteroid; PY – person-years

263 Values in bold are statistically significant

FIGURE LEGEND

Figure 1: Histogram showing the age distribution of the study subjects with ABPA.

Figure 2: Pie charts showing the age of onset of asthma in the two study groups (elderly and non-elderly asthma). The portion shaded in black represents ABPA without asthma, while the various shades of gray represent (<13 years, 13-45 years, and >45 years of age) the ages at the onset of asthma in subjects diagnosed with ABPA.

Figure 3: Violin plot depicting the distribution of serum total IgE, serum *A.fumigatus*-specific IgE, serum *A.fumigatus*-specific IgG, and total eosinophil count on the vertical axis. The horizontal axis shows the three age groups (≤ 45 , 46-59, and ≥ 60 years). The width of the violin plot is determined by the number of data points corresponding to different levels of test values. The horizontal solid line within each plot represents the median value for the observations, while the dotted line above and below the median denotes the first and third quartile. The distribution of serum total IgE ($p=0.03$) and *A.fumigatus*-specific IgE levels ($p=0.022$) was significantly different between the three groups. However, when adjusted for multiple comparisons, only the *A.fumigatus*-specific IgE was significantly lower in the ≥ 60 years subgroup than 46-59 years (asterisk). There was no statistically significant difference in total eosinophil count ($p=0.26$) and *A.fumigatus*-specific IgG ($p=0.92$) among the three groups.

Figure 4: Kaplan-Meier curve demonstrating the probability of exacerbation (vertical axis) against the duration of follow-up in days (horizontal axis). The dotted line represents the elderly subjects with ABPA, while the solid line represents the non-elderly. There was a trend towards a longer time to first ABPA exacerbation in the elderly subjects (p value=0.06, log-rank test).

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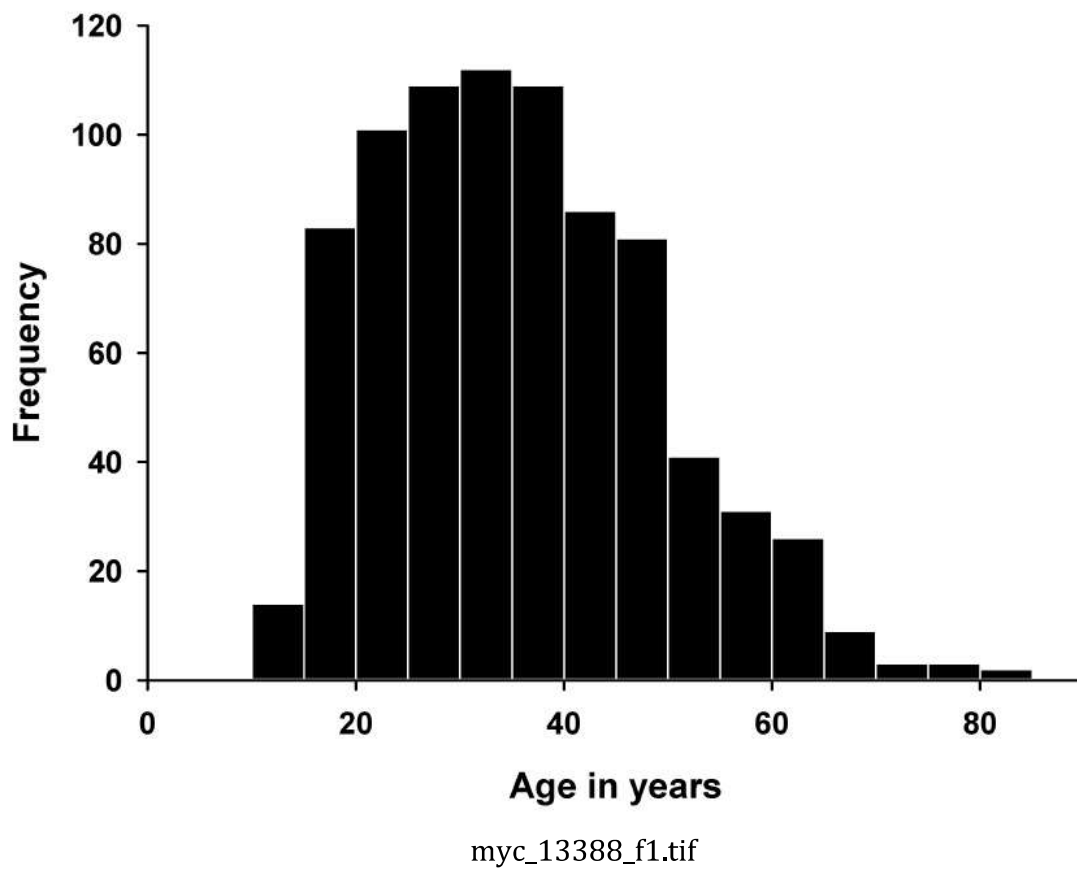
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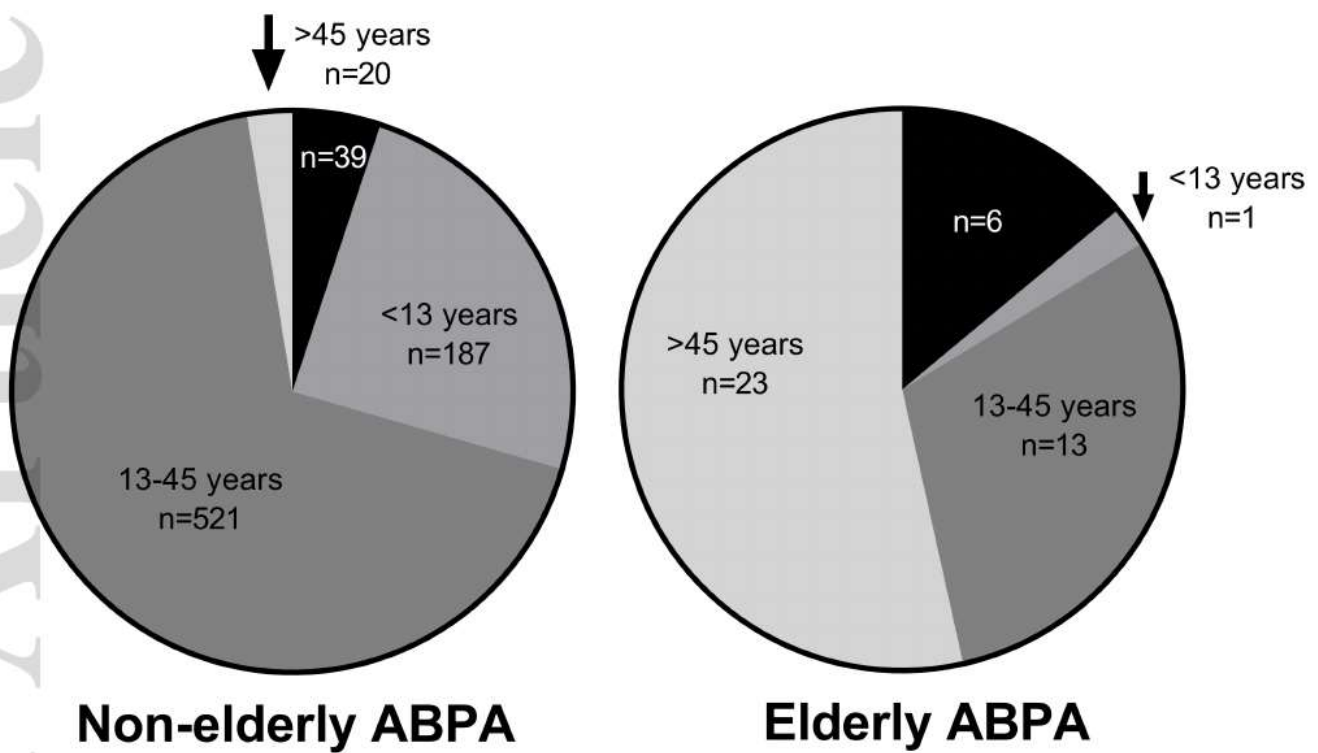
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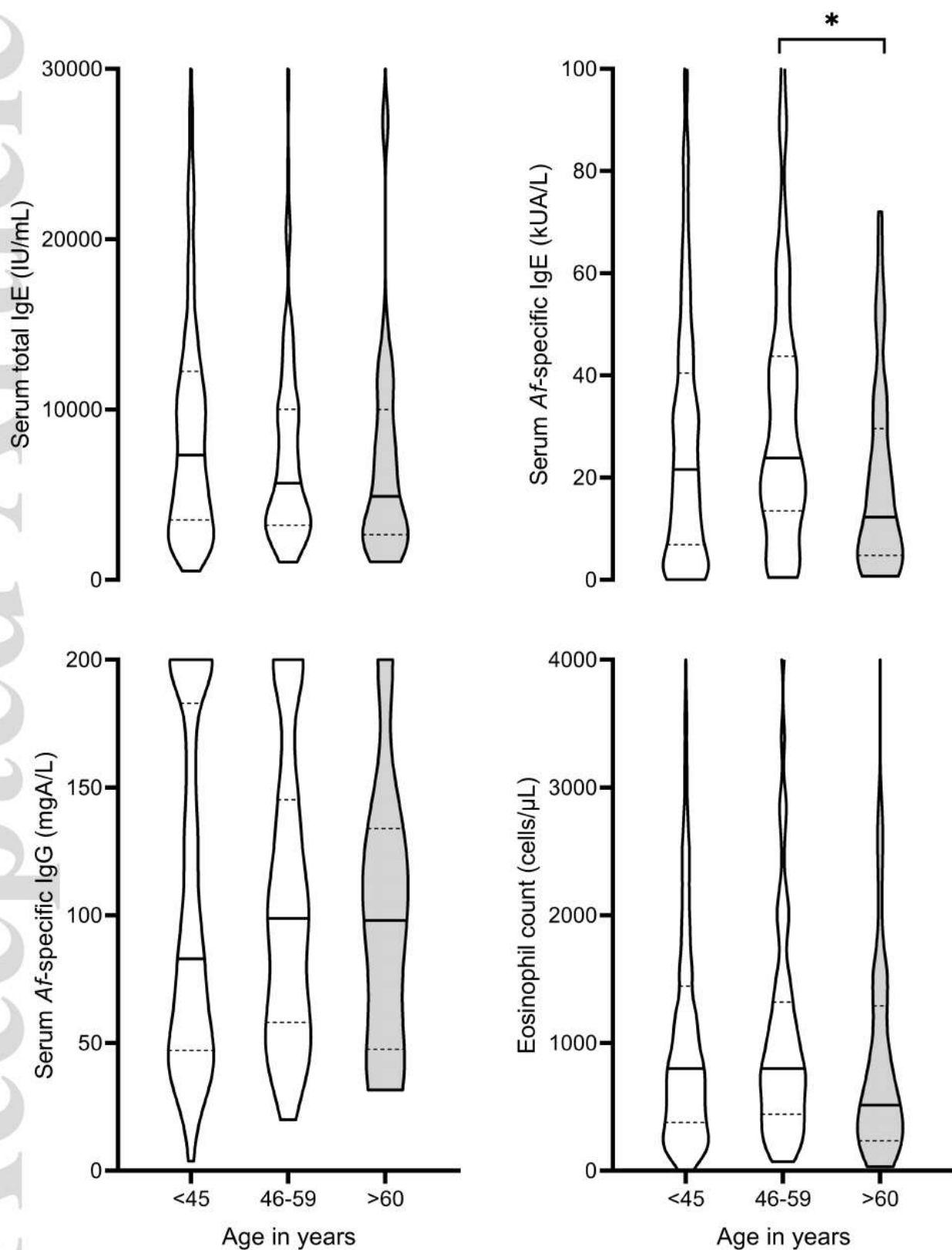
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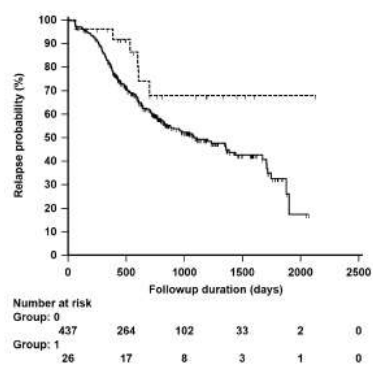


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