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Allergic bronchopulmonary aspergillosis is associated with pet ownership in Cystic Fibrosis

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Running Title: ABPA is associated with pet ownership in CF

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Allergic bronchopulmonary aspergillosis is associated with pet ownership in Cystic Fibrosis

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Abstract

Background: Late diagnosis of allergic bronchopulmonary aspergillosis (ABPA) is associated with significant lung function decline and morbidity in cystic fibrosis (CF). The association of ABPA and domestic pet ownership in patients with CF has not been elucidated yet. Our objective was to determine the association of ABPA with pet ownership in patients with CF.

Methods: Clinical and microbiological data from certified local patient registry was analyzed for 109 patients with CF aged 1-64 years: 55 pet owner and 54 non-pet owners. The primary outcome of the retrospective observational study was the occurrence of ABPA in pet owners and non-pet owners with CF. The free statistical software R was utilized to investigate logistic regression models for association factors.

Results: Of the 109 patients included in the study, 61 (56%) were female. The mean age of the total group was 25.4 ± 13.2 years. Adjusted analysis revealed that ABPA (OR 5.0227, 95% CI: 1.182-21.340, $p=0.029$) was associated with pet ownership in patients with CF. Furthermore, ABPA in pet owners with CF was associated with an increased number of exacerbations (OR 6.446, 95% CI: 1.057-39.328, $p=0.043$). Other outcomes did not significantly differ.

Conclusion: Owning a pet was associated with ABPA in patients with CF. Future prospective multicenter longitudinal studies are needed to investigate chronological causality between pet ownership, ABPA development, and pulmonary exacerbations and to determine whether these estimates are generalizable for ABPA susceptible patients beyond CF (asthma, bronchiectasis).

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Introduction

Allergic bronchopulmonary aspergillosis (ABPA) is an immunogenic lung disease affecting more than 4.8 million patients worldwide (1, 2). Allergens of *Aspergillus fumigatus* (*A. fumigatus*) are the causative determinants of this hypersensitive reaction (3, 4). ABPA in patients with cystic fibrosis (CF) occurs with a prevalence of 1-15% (5, 6) and manifests with a poorly controlled obstructive disease and recurrent pulmonary infiltrates with or without bronchiectasis. The underlying potential pathologic immune mechanisms of ABPA in CF are well described (7-9). *A. fumigatus* spores are encaptured in the luminal mucus where they are not effectively enough cleared by humoral and cellular host defense mechanisms resulting in

germination and formation of *Aspergillus* mycelia (9). Allergens released by the mycelia are recognized by toll like receptors 2 and 4 of dendritic cells (DC) and macrophages (7, 8). *A. fumigatus* antigen presenting DCs secrete chemokines, such as thymus activation related chemokine (TARC) to attract Th2 cells and regulatory T cells to pulmonary site of inflammation. This in turn results in a) the repression of an effective Th1 mediated *A. fumigatus* clearance and b) IL-4/IgE mediated bronchoconstriction, one clinical hallmark of ABPA (7, 8). TARC peaks strongly with ABPA exacerbations (10) and serves as a highly sensitive and specific immunological marker to discriminate between ABPA and non-ABPA patients with CF (11). Late or missed diagnosis of ABPA may result in severe decline of lung function, recurrent episodes of ABPA (12), steroid-dependency (13), and progression of CF disease (14). The burden of patients with ABPA is increased by potential therapeutic side effects (15, 16). Therefore, the search for potential association factors to timely initiate specific ABPA-preventive strategies is crucial for the management of the significant clinical impact of ABPA. Several contributing factors associated with ABPA in CF have already been determined, among them immunogenic (17-19), and therapeutic risk factors (20). Furthermore, environmental risk factors besides *A. fumigatus* allergens including season at ABPA diagnosis (21), environmental allergies (22), and indoor fungal contamination (23) have been found to correlate with ABPA. Preliminary results from our group indicated interspecies transmission of various pathogens between pet and patients with CF, among them *A. fumigatus* (24). The present observational study evaluated whether allergic bronchopulmonary aspergillosis, a hypersensitive reaction towards this fungal pathogen, may be increased in pet owners with CF.

Material and Methods

Subject Population and outcome

The retrospective observational cohort study was conducted at the Cystic Fibrosis Center Berlin, Germany (CFCB). 109 patients with CF with consistent and complete data (2012 to 2015), being treated at the CFCB, and not undergoing lung transplantation in the past, were eligible for statistical analysis. The primary outcome of the study was the occurrence of ABPA in pet owners and non-pet owners with CF to test the hypothesis that ABPA is associated with pet ownership in CF.

Ethical issues

Written informed consent from patient or parent of patient has been obtained before enrolment into the study. The study was approved by the Charité – Universitätsmedizin Berlin Institutional Review Board (approval ID: EA2/093/12).

Sample size determination

The study was designed as a study with independent cases and controls (one control per case). It was assumed that five explanatory variables were required to yield good results for binary outcome prediction. According to Harrell et al. (36) ten cases per variable at minimum for logistic regression modelling would yield a stable model. Thus, 50 events in the case cohort were needed leading to a total sample size of at least 100 patients for adjusted multivariate regression analysis.

Statistical Analysis

Multiple logistic regression analyses were performed to identify association factors of ABPA (yes/no) and ABPA in pet owners (yes/no). In addition to ownership of pet as primary predictor for the outcome "ABPA" the following parameters have been adjusted in the multiple regression analyses: age (in years), gender (male/female), predicted mean forced expiratory volume in one second (FEV₁(%)), body mass index (BMI) percentile, number of annual exacerbations, number of annual hospitalization, colonization with *Pseudomonas (P.) aeruginosa* (yes/no) and with *Candida (C.) albicans* (yes/no). Multiple regression analysis for subgroup "ABPA in pet owners" included adjustment for the above mentioned and the following variables: deletion of phenylalanine at position 508 of the cystic fibrosis transmembrane conductance regulator gene (CFTR delF508 homozygous/CFTR delF508 non-homozygous), total serum immunoglobulin E (IgE), colonization with *A. fumigatus* (yes,no), sensitization with *A. fumigatus* sensitization (yes,no), and outdoor pets (yes/no). To check the present data distributions, we used the graphic inspections by box plots, QQ plots and histograms. Distributions were arithmetically examined by skewness. All parameters were considered within the regression models and chosen for the final models by stepwise backward variable selection with AIC (Akaike information criterion). P values <0.05 were considered to be significant. All statistical analyses were performed using the free software R (Version 3.0.2, The R Project).

Data sources and assessment

Demographic, clinical and microbiological data was retrieved from a certified local patient registry MUKO.dok. Data on pet ownership was retrieved from patient's medical record. Pet ownership was discussed regularly during annual check-ups at the CFCB to ensure that data did not change over the course of the study. Patients living with pets "under one roof" were defined as pet owners (POs). Patients not living with a pet were designated non-pet owners (NPOs). Pathogen colonization, *A. fumigatus* sensitization, and comorbidities including ABPA were defined as occurring between the time of diagnosis of CF to the time of the last routinely performed follow-up before statistical analysis. Identification and susceptibility testing of *P. aeruginosa*, *A. fumigatus* or *C. albicans* were routinely performed by the certified hospital-associated microbiological diagnostic unit. Re-identification of *A. fumigatus* was performed by the Reference Laboratory for Cryptococcosis, Scedosporiosis and Imported Systemic Mycoses of the Robert Koch Institute Berlin, Germany. ABPA has been evaluated according to Cystic Fibrosis Foundation Consensus Conference and UK CF Trust proposed diagnostic criteria of ABPA in patients with CF (25, 26). ImmunoCap assays for the

analysis of total serum immunoglobulin E (IgE), specific *A. fumigatus* IgE, serological determination of Af-antibodies and specific IgEs against common airborne allergens such as mite, cat flakes, dog flakes, timothy, birch, and mugwort were routinely performed by the certified hospital-associated immunological diagnostic unit. Atopy was defined as a positive screening test for ≥ 0.35 kU/L specific IgE antibody to $\geq$ one inhalation allergen according to Nepomuceno and colleagues (22). Annual pulmonary exacerbations according to Bilton et al. (27) and hospitalization rates were defined as average annual number of events within the last three years before statistical analysis. Concomitant medication therapy was defined as daily administration over the previous 6 months. Intermittent therapy duration of intravenous antibiotic treatment was defined as one or more therapy courses shorter than 6 months in duration. Body mass index (BMI) and FEV₁ (% predicted) were defined as best BMI and best FEV₁ within the last three years before statistical analysis. Age was calculated at the start of statistical analysis.

Results

The baseline characteristics of the study cohort are presented in table 1. Results were retrieved for 109 eligible enrolled patients with CF. Data for non-eligible patients (n=181) revealed inconsistency with pet ownership follow-up, incompleteness for lung function, CFTR mutation status or lung transplantation. Sixty one patients with CF (56%) were female. The mean age of the total cohort was 25.4 ± 13.2 years. Fifty five patients (50.5%) owned pets (PO) and 54 patients (49.5%) did not (NPO). Most common pets reported were cats (35%), dogs (35%), rodents (17%), and reptiles (9%) (data not shown). As regards all applied concomitant medications both cohorts did not show statistically significant differences. A significant higher proportion of pet owners (65.5%) were sensitized against *A. fumigatus* in unadjusted analyses compared to non-pet owners (33.3%) (table 1). Furthermore, the sensitization status against dust mite, dog and cats was higher in pet owners compared to non-pet owners. Especially, with regards to sensitization against house dust mite (25.5% PO and 7.4% NPO) and dogs (23.6% PO vs. 5.6% NPO) the difference was significant. The occurrence of ABPA was significantly higher in POs - 20% - than in NPOs - 5.6% (p=0.049). Overall, the ABPA rate in the total cohort was as high as 12.8%. There was no significant difference in other baseline characteristics comparing PO and NPO.

The individual associations between pet ownership and the relevant outcomes were obtained after adjustment of demographic and clinical variables as shown in table 2 and figure 1 according to criteria indicated in the methodical section. As calculated by adjusted analysis (table 2) ABPA was the only variable that significantly associated with pet ownership in CF (OR 5.023, 95% CI: 1.182 - 21.340; p=0.0288) (table 2) (figure 1). We did not find any significant associations of pet ownership with FEV₁, exacerbations and hospitalizations, age, gender, BMI, *P. aeruginosa* or *C. albicans* colonization.

The following statistical calculations were performed to analyze the subgroup of pet owners that developed ABPA (n=11) vs. pet owners without ABPA (n=44). Unadjusted analysis revealed no significant difference for indicated variables (table 3) except for total serum IgE. The pet owner group with ABPA showed a median of 2000 kU/L total IgE compared to a median of 38.15 kU/L total IgE in the pet owner group without ABPA (p=0.001). Adjusted analysis revealed a statistically significant association between number of annual exacerbation and ABPA in pet owners with CF (OR 6.446, 95% CI: 1.057 – 39.328; p=0.043) – for adjusted variables please see methodical section (data not shown). There were

no associations between ABPA in pet owners and age, gender, FEV₁, BMI percentile, annual hospitalizations, total serum IgE, *P. aeruginosa* colonization, and outdoor pets.

Additional information on sensitization against airborne allergens was retrieved for 35 of 109 studied patients from routinely performed clinical visits. By comparing atopy status of both groups, unadjusted analysis showed that the difference of atopic pet owners and non-pet owners was not statistically significant (data not shown). Unadjusted analysis revealed a higher proportion of atopic patients in general that developed ABPA (26.1%) and that were Af sensitized (82.6%) than non-atopic patients (ABPA - 16.7%; Af sensitization - 58.3%) but these results did not reach statistical significance (table 4). Results of unadjusted analysis revealed no statistical significance for a correlation between atopy and ABPA in pet owners with CF (data not shown). By analyzing subgroup atopy data for sensitization against common cat or dog allergens no statistical correlation to ABPA in pet owners was seen in unadjusted model (data not shown).

Discussion

Recent data indicate that pet ownership is an environmental factor influencing the health of patients with CF. This includes case reports on pathogen transmission from pet to patients with CF and vice versa (28, 29) and a multicenter sibling study on the association of pet ownership with infection outcomes in these patients (30). Previous results from our group confirm transmission of various pathogens between pet and patients with CF, among them *A. fumigatus* (24). In the present study we examined whether the rate of allergic reactions towards this fungal pathogen such as ABPA - a state being associated with fulminant declines of lung function in CF - may be increased in pet owners with CF.

The results of the present study show a significant positive correlation between domestic pet ownership and ABPA in patients with CF. This association is important since ABPA is associated with a decline in lung function (14). The worst progression of all lung function parameters was found in patients with ABPA even surpassing the effect of chronic *P. aeruginosa* infection ($p < 0.0001$). Interestingly, ABPA was not found as a factor being associated with dog or cat exposure in a recent multicenter sibling CF study (30). An explanation for this could be that the CF population analyzed there was younger (mean age 11.8 ± 8.8) than the CF population in this study (mean age 25.4 ± 13.2). ABPA is seen rarely in children and infants (31) and is rather common in patients with CF aged 20-40 years (32). In the sibling study the ABPA rate was low (5.3%), whereas the ABPA rate in this study was 12.8%. Depending on the definition of ABPA and population studied the overall prevalence of ABPA in CF is reported at 8.9% (95% CI: 7.4 – 10.7) in the literature (33). It is striking that the sibling study did not adjust for other variables than age, gender, ethnicity and the presence of pets in multiple regression analysis. We assume that adjustment for more dependent variables perhaps would have brought associations for other outcomes, among them ABPA, to light.

In the search for potential explanations why pet exposure is associated with ABPA, we analyzed subgroups of pet owners with and without ABPA. Interestingly, our data revealed that pet owners with CF that developed ABPA were to the same extent atopic to common aero-allergens as their counterparts without ABPA. By looking specifically at sensitization against common cat or dog allergens, this status was not statistically different comparing pet owners with ABPA to control. Furthermore, we could not find statistically elevated numbers of indoor pets held in the pet owner group with ABPA compared to control. Therefore, the higher proportion of ABPA in pet owners can't neither be explained by an elevated general atopic or pet sensitization state, nor by exposure to an elevated amount of indoor *Af* spores. Interestingly, patients living with pets were significantly more sensitized against dust mite and dogs. However, data for these results are based on a small subgroup of patients only and for up to 41 non-pet owners with CF (and up to 27 pet owners with CF) no sensitization data was available. Therefore, these results have to be carefully interpreted. We assume that transmission of *A. fumigatus* from pets to their owner could be a reason for a higher ABPA rate. A fact that supports this assumption is the significantly higher proportion of pet owners that is sensitized against *A. fumigatus* compared to the non-pet owner group. This fits with the higher proportion of pet owners with CF that developed ABPA, as allergic sensitization to *A. fumigatus* is one of the hallmarks of ABPA diagnosis (26) and precedes development of ABPA (34). Pathogenic transmission from pet to owners does take place in patients with CF (29, 35) and preliminary results from our group indicated transmission of *A. fumigatus* from a rodent to a patient with CF (24). Transmission of bacterial and fungal pathogens from household pet to owner takes place through various routes such as inhalation, physical injuries (scratches), and contact with urine, faeces or contaminated environment) (35). Unpublished data from our group revealed evidence of *Aspergillus* species in the throat, rectum and/or environment (sleeping facility, pet litter etc.) of all examined pet group cats, dogs, and rodents (swab test and paddle tests). There is evidence in literature that *Aspergillus* species are typically localized in the nasal cavity of dogs. Dogs, especially with a long head and nose (dolichocephalic breeds) like German Shepherds seem to be more affected. Interestingly, in the present work we examined *A. fumigatus* in all pet group except dogs (unpublished data). From the six examined dogs (all of them with long head and nose) only in one dog *Aspergillus niger* was found. No other *Aspergillus* species were examined in these dogs. In line with that observation a Mexican prospective prevalence study on 227 stray dogs examined *A. niger* as the most often identified *Aspergillus* species (82.8%) followed by *A. flavus* (14.3%) and *A. terreus* (2.9%) (36). The authors of this Mexican study suggest careful handling with stray dogs carrying pathogenic species as they may be a reservoir for transmission of *Aspergillus* species being harmful to neonates and immunocompromised persons patients (36). Pathogenic involvement of *A. niger* in invasive pulmonary diseases has been described for the last 20 years (37). We have done multivariate subgroup regression analysis for the association for *Aspergillus* colonization as well as for ABPA with dog ownership and various pet groups (unpublished data), but no correlation was found, perhaps due to limited size of dog owners with CF in the present work. Whether these observations may have potential impact on clinical daily life remains speculative. It would be interesting to examine in future prospective studies with CF whether dog owners are at a higher risk of developing ABPA.

Adjusted multivariate regression analysis revealed a statistically significant positive correlation between pulmonary exacerbations and ABPA in patients with CF that live with pets. This finding is important because exacerbations in CF are one of the most relevant clinical events in CF and have significant impact on the survival of the patient (38). Prevention or early and vigorous treatment of exacerbations in CF are key to preserve lung function and prolong survival of the patient (39). However, the associations calculated in the present study do not allow us to establish a chronological causality between ABPA and pulmonary exacerbations in pet owners with CF. It is therefore not apparent whether ABPA (or other pulmonary infections) are the reason for the exacerbations (26) or if pulmonary exacerbations (and the intravenous antibiotic treatment for their management) are the reason for the development of ABPA. Limitations to our study include possible bias due to the retrospective design and the small number of patients which could influence the association of pet ownership and ABPA in CF. Furthermore, unmeasured confounding with immunogenic risk factors, e.g. MHC class II variants (17) and unstudied environmental risk factors could still play a role. Future prospective multicenter longitudinal studies are needed to investigate chronological causality between pet ownership, ABPA development, and pulmonary exacerbations and to determine whether these estimates are generalizable for ABPA susceptible patients beyond CF (asthma, bronchiectasis).

The results of the present retrospective observational study reveal that pet ownership in CF is associated with ABPA and that ABPA in pet owners was associated with increased odds for pulmonary exacerbations which are responsible for lung function deterioration and impaired survival in CF. It remains speculative whether interspecies fungal transmission may play a role in the established associations of ABPA and pet ownership. We did not see differences between ownership of a certain group of pets and higher risk for ABPA, perhaps due to limited patient's size but we cannot exclude such an association. In addition, due to limited access to complete data, we cannot rule out that sensitization status in pet owners may have a positive effect on ABPA development. Further prospective analyses should primarily focus on the association between pet ownership of certain groups of pet and ABPA. If future prospective studies confirm that pet ownership is a risk factor for ABPA in CF we would recommend 1) to inform patients with CF on the association of pet ownership and ABPA; 2) to regularly screen for pet ownership in ABPA patients with CF during regular clinical visits, 3) to regularly screen for ABPA in patients with CF owning a pet, and 4) to exclude pet ownership as a noxious effect for failure of ABPA therapy or recurrent ABPA episodes. In addition, especially in pet owners with CF where antibiotic treatment fails, ABPA should be excluded to prevent unnecessary antibiotic treatment with its side effects.

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document for important intellectual content: all authors; study supervision: CS; data access and responsibility: CS had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis and for the submission.

Tables

Table 1 Baseline characteristics¹ of 54 non-pet owners (CF) and 55 pet owners (CF) (total n=109)

Variable	Non-pet owners	Pet owners	P-value
Number of patients, n (%)	54 (49.5)	55 (50.5)	
Age, mean (stand. dev)	25.46 (14.80)	26.02 (13.00)	0.835
Gender, male	26 (48.1)	26 (47.3)	1.000
CFTR dF508 homozygous	26 (48.1)	37 (68.5)	0.051
BMI Percentile (median [IQR])	16.05 [5.50, 33.98]	21.20 [6.10, 36.35]	0.844
FEV ₁ (% pred.), (median [IQR])	78.50 [44.50, 101.00]	69.00 [47.00, 86.50]	0.228
Pancreatic insufficiency, n (%)	49 (90.7)	52 (94.5)	0.693
CF-related diabetes, n (%)	10 (18.5)	15 (27.3)	0.390
ABPA, n (%)	3 (5.6)	11 (20.0)	0.049
Exacerbations p.a. (median [IQR])	1.00 [1.00, 2.00]	1.00 [1.00, 2.00]	0.878
Hospitalizations p.a. (median [IQR])	1.00 [0.00, 2.00]	1.00 [0.00, 2.00]	0.436
Total IgE (median [IQR]) (kU/L)	57.85 [20.12, 297.50]	53.28 [23.49, 278.16]	0.519
<i>P. aeruginosa</i> colonization, n (%)	26 (48.1)	32 (58.2)	0.391
<i>A. fumigatus</i> colonization, n (%)	11 (20.4)	15 (27.3)	0.535
<i>C. albicans</i> colonization, n (%)	29 (53.7)	30 (54.5)	1.000
<i>A. fumigatus</i> sensitization, n (%)	18 (33.3)	36 (65.5)	0.002
unknown status ²	1 (1.9)	1 (1.8)	n.a.
House dust mite sensitization, n (%)	4 (7.4)	14 (25.5)	0.0185 ³
unknown status ² , n (%)	41 (75.9)	25 (45.5)	n.a.
Dog sensitization, n (%)	3 (5.6)	13 (23.6)	0.0130 ³
unknown status ² , n (%)	39 (72.2)	27 (49.1)	n.a.
Cat sensitization, n (%)	5 (9.3)	13 (23.6)	0.0691
unknown status ² , n (%)	40 (74.1)	26 (47.3)	n.a.
Abx, <i>per os</i> , n (%)	25 (46.3)	28 (50.9)	0.703
Azithromycin, <i>per os</i> , n (%)	23 (42.6)	26 (47.3)	0.701
Abx, inhaled, n (%)	25 (46.3)	33 (60)	0.181
Abx, intravenous ⁴ , n (%)	26 (48.1)	22 (40)	0.443
Steroids, <i>per os</i> , n (%)	8 (14.8)	8 (14.5)	1.000
Antimycotica, n (%)	5 (9.3)	6 (10.9)	1.000
Dornase alfa (DNase), inhaled, n (%)	40 (74.1)	41 (74.5)	1.000

IQR: interquartile range, n: number, p.a.: per annum; %: percent; stand. dev: standard deviation, ¹including bacterial colonization, antimicrobial, and steroidal exposure; Abx: antibiotic therapy; p.o.: per os; i.v.: intravenous; DNase: desoxyribonuclease; per os; ²unknown status: sensitization status not known; ³significance is based on data representing a small subgroup of patients, see discussion; ⁴intermittent therapy

Table 2 Adjusted odds ratios for association factors of pet ownership

Variables	OR	LCL	HCL	P-value
Age (years)	0.9923	0.9611	1.0246	0.6376
Gender, male	0.7752	0.3385	1.7749	0.5468
FEV ₁ (% pred.)	0.9896	0.9732	1.0063	0.2217
BMI Percentile	0.9972	0.9772	1.0175	0.7842
Exacerbations p.a.	0.7705	0.5187	1.1446	0.1967
Hospitalizations p.a.	1.1327	0.7422	1.7287	0.5635
ABPA	5.0227	1.1822	21.3402	0.0288
<i>P. aeruginosa</i> colonization	1.4522	0.6151	3.4283	0.3946
<i>C. albicans</i> colonization	0.79	0.322	1.9384	0.6068

HCL: higher confidence limit; LCL: lower confidence limit; n: number; OR: odds ratio; p.a.: per annum

Table 3 Baseline characteristics of pet owners without ABPA and with ABPA (total n = 55)

Variable	No ABPA	ABPA	P-value
Number of patients, n (%)	44	11	
Age, mean (stand. dev)	26.55 (14.29)	23.91 (5.30)	0.552
Gender, male, n (%)	20 (45.5)	6 (54.5)	0.839
CFTR dF508 homozygous, n (%)	30 (68.2)	7 (70.0)	1.000
FEV ₁ (% pred.) (median [IQR])	70.00 [47.00, 86.25]	69.00 [50.00, 81.50]	0.883
BMI percentile (median [IQR])	17.15 [3.60, 31.80]	30.90 [22.90, 50.00]	0.051
Pancreatic insufficiency, n (%)	42 (95.5)	10 (90.9)	1.000
CF-related diabetes, n (%)	13 (29.5)	2 (18.2)	0.705
Exacerbations p.a. (median [IQR])	1.00 [1.00, 2.00]	2.00 [1.00, 3.50]	0.216
Hospitalizations p.a. (median [IQR])	1.00 [0.00, 2.00]	1.00 [0.50, 1.50]	0.557
Total IgE (median [IQR]) (kU/L)	38.15 [20.12, 137.25]	2000.00 [218.50, 3085.00]	0.001
<i>P. aeruginosa</i> colonization, n (%)	25 (56.8)	7 (63.6)	0.946
<i>A. fumigatus</i> sensitization, n (%)	26 (59.1)	10 (90.9)	0.103
<i>A. fumigatus</i> colonization, n (%)	13 (29.5)	2 (18.2)	0.705
<i>C. albicans</i> colonization, n (%)	21 (47.7)	9 (81.8)	0.091
Outdoor pets, n (%)	20 (45.5)	4 (36.4)	0.838

IQR: interquartile range, n: number, p.a.: per annum; %: percent; stand. dev: standard deviation

Table 4 Baseline characteristics of non-atopic and atopic patients with CF (total n=35)

Variable	No atopy	Atopy	P-value
Number of patients, n (%)	12	23	
Age, mean (stand. dev)	25.50 (9.27)	20.00 (11.48)	0.357
Gender, male, n (%)	7 (58.3)	8 (34.78)	0.283
CFTR dF508 homozygous, n (%)	9 (75)	16 (69.56)	1.000
FEV ₁ (% pred.), (median [IQR])	65 [54.50, 89.50]	69.00 [44.00, 86.00]	0.911
ABPA	2 (16.67)	6 (26.09)	0.686
<i>P. aeruginosa</i> colonization, n (%)	7 (58.3)	12 (52.17)	1.000
<i>A. fumigatus</i> sensitization, n (%)	7 (58.3)	19 (82.61)	0.220

IQR: interquartile range, n: number; %: percent; stand. dev: standard deviation

Figure Legend

Fig.1: Association factors of pet ownership (odds-ratio plot). *P. aeruginosa*: *Pseudomonas aeruginosa*; *C. albicans*: *Candida albicans*.

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