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Original Research

Pulmonary Aspergillosis: Epidemiology and unresolved diagnostic challenges - insights from a two-year retrospective cohort study in Marseille

Thi Quynh Pham [a,b], Léa Delorme [b,c], Sébastien Cortaredona [a,b,d], Stéphane Ranque [a,b,e], Estelle Menu [a,b,e,*]

[a] Aix Marseille Univ, SSA, RITMES, Marseille, France
[b] IHU-Méditerranée Infection, Marseille, France
[c] Assistance Publique-Hôpitaux de Marseille (AP-HM), Marseille, France
[d] Aix-Marseille Univ, IRD, SSA, MINES, Marseille, France
[e] Assistance Publique-Hôpitaux de Marseille (AP-HM), Service de Parasitologie Mycologie, Marseille, France

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ABSTRACT

Objective: *Aspergillus* spp. are ubiquitous fungi that cause invasive pulmonary aspergillosis (IPA), chronic pulmonary aspergillosis (CPA), allergic bronchopulmonary aspergillosis (ABPA), and some other less common forms depending on the immune status of the host. This study aimed to evaluate the epidemiology and clinical diagnosis of *Aspergillus*-related diseases at the University Hospital of Marseille (AP-HM).
Methods: We performed a retrospective cohort study of patients treated at the AP-HM between January 2022 and December 2023. *Aspergillus*-specific serologic tests (IgG, IgE) and galactomannan antigen (GM) tests were integrated with clinical, imaging data from patients' medical records. Diagnostic frameworks were established based on the standard diagnostic criteria to identify IPA, CPA, and ABPA.
Results: Of 2412 patients with GM testing, 46 (1.9 %) had IPA. Of 2889 patients with *Aspergillus*-specific IgG testing, 16 (0.6 %) were diagnosed with CPA. Of 1779 patients with *Aspergillus*-specific IgE testing, 46 (2.6 %) were diagnosed with ABPA. We noted biotherapy (tocilizumab and oblinutuzumab) as potential emerging risk factors for IPA. Strikingly, only 10 of 46 patients with ABPA were treated by physicians, highlighting potential gaps in clinical practice and current diagnostic guidelines. The 3-month case fatality rate was 46.7 % for IPA, 13.3 % for CPA and 0 for APBA. Despite treatment, 13 % of patients with ABPA experienced an exacerbation.
Conclusions: This study highlights the prevalence of *Aspergillus*-related lung disease and the high 3-month mortality rate in IPA and CPA in AP-HM. Discrepancies in ABPA diagnosis highlight the need for improved diagnostic algorithms that better reflect real-world clinical practice and address these challenges.

1. Introduction

Aspergillus species are ubiquitous saprophytic fungi found in the environment that can cause a variety of human pulmonary diseases. Due to the small size of their conidia, *Aspergillus* spores are easily inhaled, making the lung the primary target organ for infection [1,2]. The clinical presentation of *Aspergillus*-related lung diseases (ARLD) is highly variable, depending on the severity of the infection and the immune status of the host, and is therefore classified into three main forms: invasive pulmonary aspergillosis (IPA), chronic pulmonary aspergillosis (CPA), and allergic bronchopulmonary aspergillosis (ABPA), as well as some other less common forms [3]. IPA primarily affects severely immunocompromised individuals and has recently been increasingly observed in critically ill patients with severe COVID-19 or influenza pneumonia complicated by acute respiratory distress syndrome (ARDS) [4–6]. CPA is a spectrum of locally invasive disease that typically occurs in patients with mild immunodeficiency, chronic lung disease, or pre-existing lung cavities such as those seen after tuberculosis, sarcoidosis, emphysema, or lung surgery [4,7]. In contrast, ABPA, known as an immune-mediated inflammatory response caused by hypersensitivity to *Aspergillus*, is most commonly seen in patients with asthma or cystic fibrosis (CF) [4,8].

Worldwide, it is estimated that there are approximately 250,000 new cases of IPA annually, 3 million cases of CPA, and 4.8 million cases of

* Corresponding author. Service de Parasitologie-Mycologie, AP-HM, 19-21 Boulevard Jean Moulin, 13005 Marseille, France.
E-mail address: estelle.menu@ap-hm.fr (E. Menu).

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ABPA per year in asthmatic populations [9]. However, data on the epidemiology of ARLD in France remain scarce and often focus on specific disease presentations [10–12]. The evolution of diagnostic criteria in recent years has made the diagnosis of pulmonary aspergillosis challenging [5,6], especially since the ABPA diagnostic criteria have been revised three times in four years [8,13,14]. The emergence of new risk factors, such as COVID-19, has led to further updates in guidelines for the diagnosis of IPA [5]. In addition, the ecological diversity and regional climate variations in France, which influence the prevalence and distribution of *Aspergillus* species, highlight the need for localized epidemiological data [10,15,16]. In France, we are faced with a climatic diversity within the territory that could influence the diversity of ARLD. For example, the climate of Marseille is characterised by dry conditions and strong winds, which is very different from the temperate climate of northern France [17]. Despite this, to the best of our knowledge, no studies have investigated the prevalence of all three forms of ARLD, including IPA, CPA, and ABPA, in Marseille. Therefore, this study aims to evaluate the epidemiology of pulmonary aspergillosis in the University Hospital of Marseille.

2. Methods

2.1. Study design

This retrospective cohort study was conducted at AP-HM, comprising four tertiary hospitals in Marseille with a total of 3300 beds: North Hospital, La Timone Hospital, La Conception Hospital, and South Hospital. The study took place between January 2022 and December 2023. [18]. The study protocol and ethical criteria were approved by the Scientific Ethics Committee of the Assistance Publique-Hôpitaux de Marseille (PADS 24-39-dgr). Reporting adhered to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement to ensure methodological rigor and transparency (Supplementary Material 1).

2.2. Serological test screening procedure

The following serologic data were collected: *A. fumigatus*-specific IgG (Gm3) and IgE concentrations measured by the commercial ImmunoCAP system (Phadia, Thermo Fisher Scientific, USA), and galactomannan antigen (GM) detected by ELISA using the Bio-Rad Platelia *Aspergillus* Antigen (Bio-Rad, Marnes-la-Coquette, France).

2.3. Selection criteria

To identify IPA patients, we selected patients with a positive GM test index (i.e. $\geq$ 0.5 in serum and $\geq$1.0 in broncho-alveolar lavage (BAL)). To identify CPA patients and ABPA patients, we selected patients with a positive *Aspergillus*-specific IgG test (i.e. $>$ 27 mgA/L), and a positive *Aspergillus*-specific IgE test (i.e. $\geq$ 0.35 kUA/L), respectively. Seropositivity cut-off values were determined according to the recommended diagnostic criteria for each form of pulmonary aspergillosis [5,7,8,13,19].

2.4. Patients' data

2.4.1. Medical reports

All medical reports of selected patients recorded in Axigate DPI (version 5.11.3P10.8.3) were analysed and the following data were obtained when available. Data entry and processing was performed using MS Excel 2013 software.

2.4.2. Socio-demographic characteristics, potential risk factors, and clinical features

Age, sex, body mass index and potential risk factors were recorded for all participants (Supplementary Material 2). Clinical characteristics of patients included: fever refractory to broad-spectrum antibiotics, cough, haemoptysis, pleuritic chest pain, and dyspnea.

2.4.3. Mycological features

We collected data on *Aspergillus* Western Blot IgG kit (LDBio, Lyon, France), *Aspergillus* PCR, positive *Aspergillus* culture on Sabouraud dextrose agar supplemented with gentamicin and chloramphenicol (Bio-Rad, Marnes-la-Coquette, France) and eosinophil cell counts.

2.4.4. Imaging features

Imaging findings were extracted from the Centricity™ software (version 6.0 SP11.2.3, GE Healthcare, USA) and included all details of the techniques used (chest X-ray or high-resolution computed tomography) in patients with pulmonary aspergillosis and the imaging features: condensation, ground-glass opacities, reticular opacity, pleural effusion, nodules, micronodules, halo sign, reverse halo sign, cavities, fibrosis, emphysema, bronchiectasis, cavities, fungus ball, mucoid impaction and high-attenuating mucus.

Central bronchiectasis is defined as the dilatation of the proximal (central) bronchi near the lung hilum. The peripheral airways tend to be relatively unaffected on HRCT [20].

2.4.5. Clinicians' diagnosis

Diagnoses of ARLD were made independently and based on established criteria. We also noted whether the treating clinicians had initially considered ARLD, in order to assess the consistency between clinical suspicion and standardised diagnosis.

2.4.6. Outcome

Data on survival or death were collected at 1-month and 3-month. ABPA patient outcomes, including stability or exacerbations, were collected at 12-month.

2.5. Classification

Patients in this study were classified according to the latest recommendations (Fig. 1) as follows:

- *IPA* was defined according to the EORTC/MSG 2019 diagnostic criteria [19].
- *CAPA* (COVID-associated pulmonary aspergillosis) was defined according to the ECMM/ISHAM 2020 criteria for COVID-associated IPA [5].
- *IAPA* (Influenza-associated pulmonary aspergillosis) was defined according to the expert case definitions for influenza-associated IPA [6].
- *CPA* was defined according to the ESMID 2016 criteria [7].
- *ABPA* was defined according to the modified ISHAM 2020, ASANO 2021 diagnostic criteria [8,13].
- *ABPA* exacerbation was defined as a worsening of respiratory clinical (e.g., increased cough, dyspnea, expectoration of mucus plugs) and/or radiological worsening. These episodes were often associated with a rise in total serum IgE levels, radiographic changes (such as new infiltrates or mucus impaction), or both [21].
- *Aspergillus* sensitisation (AS) was defined by the presence of elevated levels of *Aspergillus*-specific IgE antibodies ($\geq$0.35 kAU/l) in a patient typically well controlled with appropriate asthma treatment [22].
- *SAFS (Severe asthma with fungal sensitisation)* was defined by AS in an uncontrolled asthmatic patient with total IgE $<$1000 IU/ml who doesn't meet the criteria for ABPA [22].
- *Aspergillus* colonisation (AC) was defined by the presence of two positive *Aspergillus* cultures from lower respiratory tract samples on two separate occasions within 6 months in a patient who is asymptomatic and who doesn't require antifungal treatment [23].

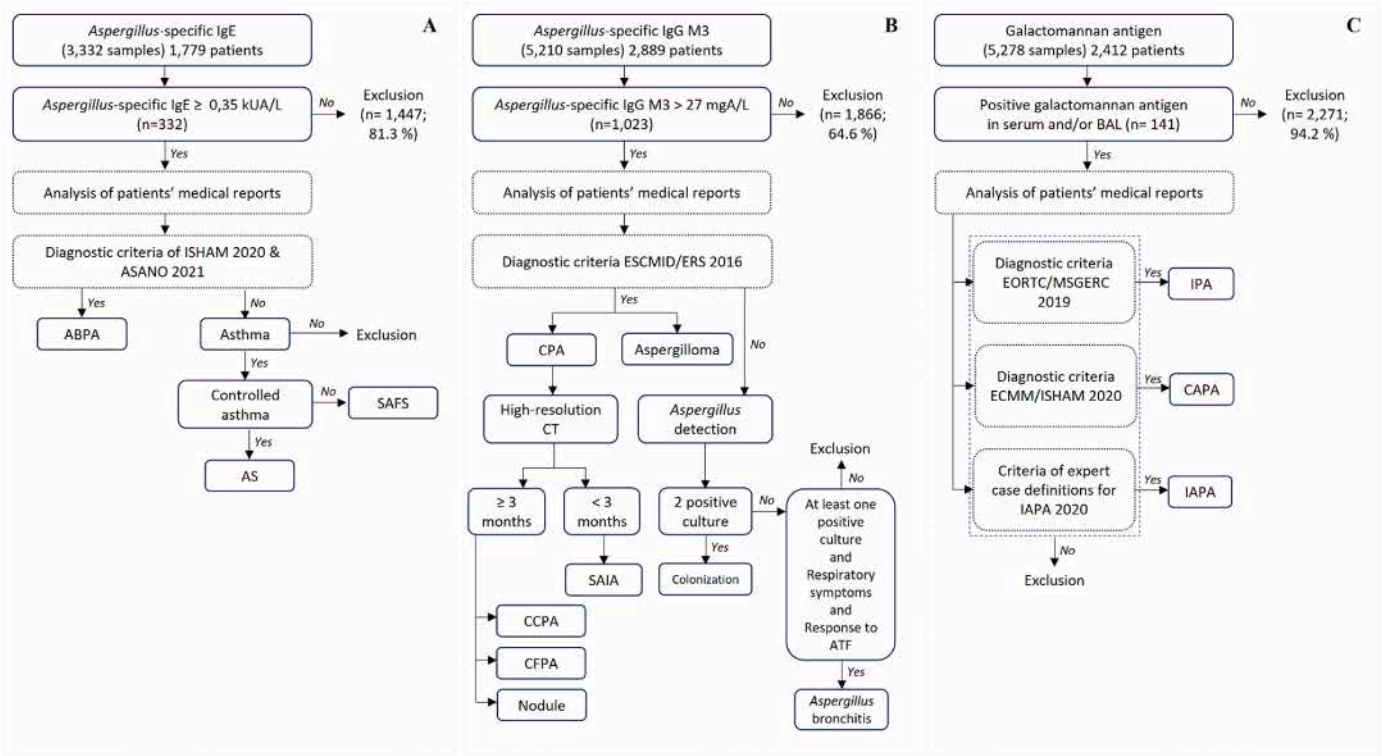

Fig. 1. Classification scheme for pulmonary aspergillosis (A: ABPA patients, B: CPA patients, C: IPA patients).
Abbreviations: AP-HM = Assistance Publique–Hôpitaux de Marseille, CT = computed tomography, AS = *Aspergillus* sensitisation, SAFS = Severe asthma with fungal sensitivity, ABPA = Allergic bronchopulmonary aspergillosis, ISHAM = International Society of Human and Animal Mycology, CPA = chronic pulmonary aspergillosis, SAIA = Subacute invasive aspergillosis, CCPA = Chronic cavitary pulmonary aspergillosis, CFPA = Chronic fibrosis pulmonary aspergillosis, ESCMID = European Society for Clinical Microbiology and Infectious Disease, BAL = Bronchoalveolar lavage, IPA = Invasive pulmonary aspergillosis, EORTC = European Organization for Research and Treatment of Cancer, ECMM = European Confederation of Medical Mycology, CAPA = COVID-associated pulmonary aspergillosis, IAPA = Influenza-associated pulmonary aspergillosis, ATF = antifungal.

- *Aspergillus* bronchitis (AB) is a superficial fungal infection of the lower respiratory tract that doesn't meet the diagnostic criteria for other forms of ARLD and may respond to antifungal treatment [24].

2.6. Statistical analysis

2.6.1. Grouping and analysis Steps

Step 1: Patients were categorised into two groups: the invasive group (IPA and CPA) and the allergic group (ABPA). This classification assessed differences in risk factors, clinical symptoms, and disease severity between the invasive and allergic groups.
Step 2: Within the invasive characteristic group, patients were divided into acute invasive pulmonary aspergillosis and chronic pulmonary aspergillosis subgroups. Comparative analyses were performed to identify detailed differences in risk factors, clinical presentation, and outcome between the acute and chronic subgroups.

2.6.2. Analysis methods

Bivariate analyses were performed to assess differences between the invasive group "IPA + CPA" and the allergic group "ABPA", as well as between the acute presentation "IPA" and the chronic presentation "CPA". Fisher's exact test was used to compare qualitative variables, while Mann-Whitney *U* test was used for quantitative variables. Principal component analysis (PCA) was also performed. Missing values were imputed with the PCA model (Supplemnetary Material 3).

All statistical analyses were performed using SAS 9.4 software (SAS Institute, Cary, NC), except for PCA, which was performed using R (FactoMineR package). Statistical significance was defined as $p < 0.05$ (Supplementary Material 3).

3. Results

During the 2-year study period, we diagnosed 46 cases of IPA, 16 cases of CPA, and 46 cases of ABPA at the AP-HM according to the recommended criteria (Fig. 2, Table 1).

3.1. ARLD epidemiological picture

Of the 2412 patients who underwent galactomannan antigen testing, 141 tested positive in serum and/or BAL. Using the EORTC/MSG 2019 criteria for IPA, the ECMM/ISHAM 2020 criteria for CAPA identification, and IAPA expert criteria [5,6,19], we identified 46 (1.9 %) IPA patients, including 5 CAPA patients and 1 IAPA patient. Among these IPA patients, 12 underwent biopsy procedures following physician consideration and one case was histologically confirmed. In total, we identified one (2.2 %) histologically proven IPA, 28 (60.9 %) probable IPA, and 17 (37.0 %) possible IPA.

Of the 2889 patients who underwent *Aspergillus*-specific IgG M3 testing, 1023 were positive. Using the 2016 ESMID/ERS criteria [7], we identified 16 (0.6 %) patients with CPA.

Of the 1779 patients who underwent *Aspergillus*-specific IgE testing, 332 were positive. Using the modified 2020 ISHAM and 2021 ASANO diagnostic criteria [8,13], we identified 46 (2.6 %) patients with ABPA.

This methodological approach identified other ARLD, including 17 patients with SAFS, 11 with AS, 6 with AB, 19 with AC and 3 simple aspergillomas within 2 years.

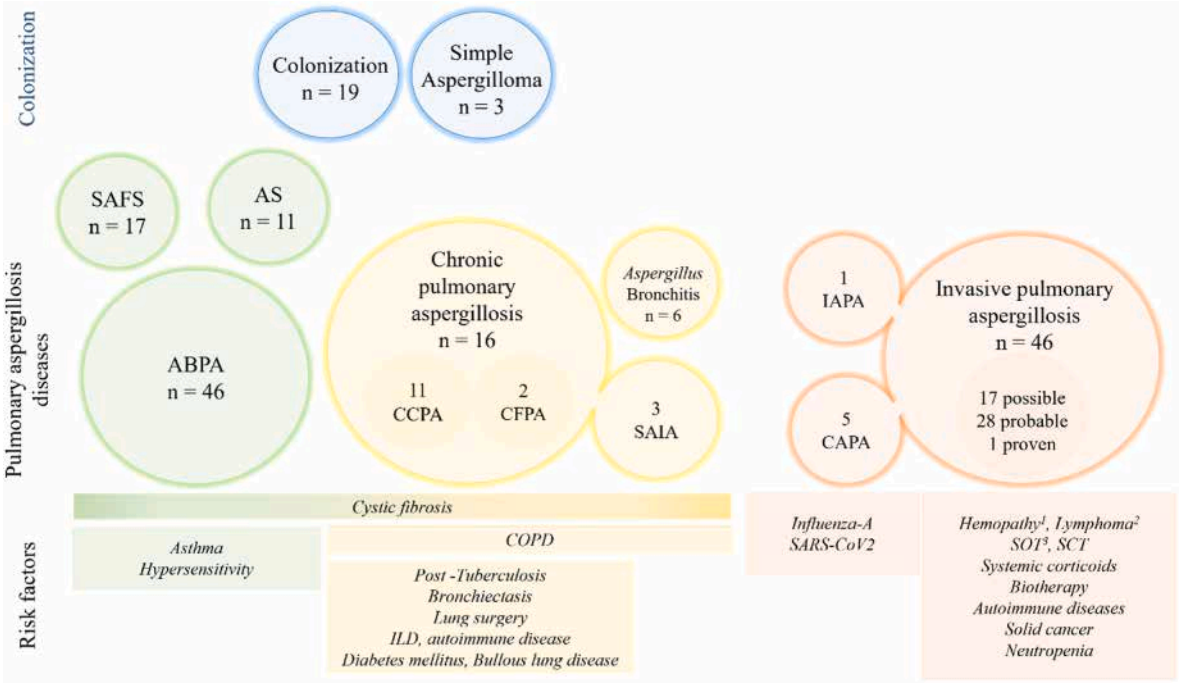

Fig. 2. Synthetic graph showing the number of patients diagnosed with *Aspergillus*-related lung disease at the AP-HM in 2022–2023 and their corresponding hosts and risk factors.

Abbreviations: AS = *Aspergillus* sensitisation; SAFS = severe asthma with fungal sensitivity; COPD = Chronic Obstructive Pulmonary Disease; ILD = Interstitial lung disease; CCPA= Chronic cavitary pulmonary aspergillosis; CFPA = Chronic fibrosis pulmonary aspergillosis; SAIA = Subacute invasive aspergillosis; IAPA = Influenza-associated pulmonary aspergillosis; CAPA = COVID-associated pulmonary aspergillosis; SOT = Single organ transplantation; [1] Acute myeloid leukemia; acute lymphoblastic leukemia, myelodysplasia syndrome, bone marrow aplasia; [2] non-Hodgkin B lymphoma, diffuse large cell B lymphoma; [3] lung, heart, kidney, liver; SCT = Stem cell transplantation.

3.2. Patient sociodemographics and comorbidities

Regarding demographic characteristics, the mean age was significantly lower in the patients with allergic ARLD (34.4 ± 20.6 years) than in those with invasive ARLD (53.24 ± 18.9 years; $p < 0.001$), while gender distribution and BMI showed no statistically significant differences. Among comorbidities, CF was the most prominent comorbidity in the allergic ARLD patients, affecting 63.0 % of patients compared to 8.1 % in the invasive group ($p < 0.001$). Asthma was also strongly associated with the allergic ARLD, affecting 28.3 % of patients compared to 3.2 % in the invasive ARLD patients ($p = 0.001$). In contrast, immunosuppressive comorbidities such as solid organ transplant, stem cell transplant, haematological malignancy, chronic obstructive pulmonary disease, biotherapy, chemotherapy and cardiovascular disease were significantly more common in the invasive ARLD patients than in the allergic ARLD patients ($p < 0.01$). Using immunomodulating monoclonal antibodies (tocilizumab, obinutuzumab, and rituximab), a potential risk factorwas observed exclusively in IPA patients. In fact, 15.2 % of IPA patients were receiving biotherapy including 71.4 % receiving rituximab, 14.3 % receiving obinutuzumab, and 14.3 % receiving tocilizumab. These treatments were not found in CPA or ABPA cases.

When comparing the invasive ARLD patients subgroups, a significantly higher prevalence of solid organ transplantation (i.e. lung, heart, kidney and liver) and stem cell transplantation (54.4 %) was observed in IPA compared to CPA (12.5 %; $p < 0.01$). Haematological malignancies (14.5 %) and biotherapy (11.3 %) were seen exclusively in the IPA group. The prevalence of bronchiectasis was significantly higher in the CPA group than in the IPA group (50.0 %, $p = 0.001$). A history of tuberculosis, lung surgery and pulmonary aspergillosis showed a significant association with CPA ($p < 0.05$).

3.3. Clinic and imaging features

In terms of common clinical symptoms, cough and dyspnoea were predominant in all three groups of ARLD patients, with no statistically significant difference observed between the groups. In contrast, fever had a significantly higher prevalence in invasive (37.7 %) compared to allergic ARLD patients (2.2 %; $p = 0.001$). This disparity was emphasised by the subgroup analysis of invasive ARLD patients, which showed a prevalence of 45.7 % in IPA compared to 13.3 % in CPA ($p < 0.05$). Similarly, weight loss was reported more frequently in the invasive group (22.6 %) compared to allergic ARLD patients (6.5 %; $p < 0.05$). When comparing IPA and CPA patients, haemoptysis was significantly more common in CPA (37.5 %) compared to IPA (2.2 %; $p = 0.001$).

On imaging, ground-glass opacities and consolidations were the predominant findings in invasive compared to allergic ARLD patients ($p < 0.001$). Interestingly, pleural effusion (23.9 %), halo sign (13 %), and reversed halo sign (6.5 %) were observed exclusively in IPA, whereas fungal balls were observed exclusively in CPA (56.3 %) and mucoid impaction in ABPA patients (26.1 %) (Supplementary Material 3). Central bronchiectasis was significantly more common in allergic patients (69.6 %) than in invasive ARLD patients (17.7 %; $p < 0.001$) (Supplementary Material 3). Among ABPA patients, 69.6 % (32/46) met the radiological criteria for central bronchiectasis. Additionally, 65.6 % (21/32) of those with central bronchiectasis showed upper- or mid-lung predominant involvement (e.g., upper only, upper and middle lobes). Among invasive ARLD patients, bronchiectasis was significantly more common in CPA than in IPA ($p = 0.004$).

3.4. Aspergillus culture

Culture results showed that *Aspergillus* species were the most commonly detected in all three ARLD patient groups (IPA, CPA and ABPA), with positive rates of 54.8 %, 68.8 % and 52.0 %, respectively.

Table 1
Characteristics of patients with *Aspergillus*-related lung diseases (ARLD) in a 2-year retrospective study.

	ARLD					Subgroup invasive ARLD				
	Invasive		**Allergy**		**p-value***	**Acute**		**Chronic**		**p-value***
	IPA + CPA		**ABPA**			**IPA**		**CPA**		
	(n=62)		**(n=46)**			**(n=46)**		**(n=16)**		
	n	%	n	%		n	%	n	%	
Demographic										
Age (mean ± SD, min-max)	53.24 ± 18.9	4–81	34.6 ± 20.6	5–76	**<0.001**	53.5 ± 19.0	4–81	52.5 ± 19.1	15–75	0.785
Sex (% males)	39	62.9	22	47.8	0.169	27	58.7	12	75	0.369
BMI (mean ± SD, min-max)	23.0 ± 5.9	13–42	20.7 ± 4.9	11–35	0.061	23.8 ± 6.2	13–42	20.5 ± 4.0	16–29	**0.049**
Comorbidity										
Solid organ transplantation & Stem-cell transplantation	27	43.5	8	17.4	**0.006**	25	54.4	2	12.5	**0.004**
Autoimmune disease	14	22.6	16	34.8	0.195	10	21.7	4	25	0.743
Diabetes mellitus	10	16.1	9	19.6	0.799	10	21.7	0	0	0.052
Hematologic malignancy	9	14.5	0	0	**0.010**	9	19.6	0	0	0.096
Chronic obstructive pulmonary disease	12	19.4	2	4.4	**0.023**	8	17.4	4	25	0.488
Interstitial lung disease	11	17.7	0	0	**0.002**	8	17.4	3	18.8	1.000
Solid cancer	9	14.5	2	4.4	0.112	6	13	3	18.8	0.683
Biotherapy risk factor (immunomodulating monoclonal antibodies)	7	11.3	0	0	**0.020**	7	15.2	0	0	0.175
(anti-CD20) Rituximab	5	71.4	–	–		5	71.4	–	–	
(*anti*-IL6) Tocilizumab	1	14.3	–	–		1	14.3	–	–	
(anti - CD20) Obinutuzumab	1	14.3	–	–		1	14.3	–	–	
Chemotherapy	10	16.1	0	0	**0.005**	8	17.4	2	12.5	1.000
Hepatitis, chronic alcoholism	4	6.5	2	4.4	1.000	4	8.7	0	0	0.565
Bronchiectasis	12	19.4	12	26.1	0.485	4	8.7	8	50	**0.001**
Cystic fibrosis	5	8.1	29	63	**<0.001**	3	6.5	2	12.5	0.597
Neutropenia	2	3.2	0	0	0.506	2	4.4	0	0	1.000
Severe COVID 19	5	8.1	0	0	0.070	5	10.9	0	0	0.315
Severe Influenza A	1	1.6	0	0	1.000	1	2.2	0	0	1.000
Asthma	2	3.2	13	28.3	**<0.001**	**1**	2.2	1	6.3	0.453
Cardiovascular disease	28	45.2	9	19.6	**0.007**	21	45.7	7	43.8	1.000
Chronic kidney disease	7	11.3	4	8.7	0.756	6	13.0	1	6.3	0.666
History										
Pulmonary aspergillosis history	10	16.1	9	19.6	0.799	4	8.7	6	37.5	**0.014**
Lung surgery	6	9.7	9	19.6	0.167	2	4.4	4	25	**0.034**
Tuberculosis history	3	4.8	1	2.2	0.635	0	0	3	18.8	**0.015**
Allergic history	13	21.0	14	30.4	0.272	8	17.4	5	31.3	0.291
Clinical characteristic										
Cough	59	95.2	39	84.8	0.094	43	93.5	16	100	0.562
Dyspnea	48	77.4	31	67.4	0.277	37	80.4	11	68.8	0.488
Fever (nmiss = 1)	23	37.7	1	2.2	**<0.001**	21	45.7	2	13.3	**0.033**
Weight loss	14	22.6	3	6.5	**0.032**	7	15.2	7	43.8	**0.034**
Haemoptysi	7	11.3	2	4.4	0.296	1	2.2	6	37.5	**0.001**
Chest pain	0	0.0	1	2.2	0.426	0	0	0	0	–
Imaging characteristic										
Ground glass opacity, reticular opacity	42	67.7	7	15.2	**<0.001**	33	71.7	9	56.3	0.353
Consolidation	43	69.4	15	32.6	**<0.001**	33	71.7	10	62.5	0.538
Pleural effusion	11	17.7	0	0	**0.002**	11	23.9	0	0	0.052
Nodules	9	14.5	3	6.5	0.230	7	15.2	2	12.5	1.000
Fibrosis	12	19.4	0	0	**0.001**	7	15.2	5	31.3	0.268
Halo sign	6	9.7	0	0	**0.037**	6	13	0	0	0.325
Cavity	21	33.9	0	0	**<0.001**	6	13	15	93.8	**<0.001**
Emphysema	10	16.1	0	0	**0.005**	6	13	4	25	0.266
Micronodule	5	8.1	5	10.9	0.741	5	10.9	0	0	0.315
Central bronchiectasis	11	17.7	32	69.6	**<0.001**	4	8.7	7	43.8	**0.004**
Reverse halo sign	3	4.8	0	0	0.260	3	6.5	0	0	0.562
Fungal ball	9	14.5	0	0	**0.010**	0	0	9	56.3	**<0.001**
Pleural lesion	6	9.7	0	0	**0.037**	1	2.2	5	31.3	**0.003**
Mucoid impaction	0	0.0	12	26.1	**<0.001**	0	0	0	0	–
Biological results										
Aspergillus culture (n)	47		25			31		16		
Aspergillus culture Positive	28	59.6	13	52	0.620	17	54.8	11	68.8	0.532
A. fumigatus	19	67.9	10	76.9	0.719	12	70.6	7	63.6	1.000
Other**	9	32.1	3	23.1		5	29.4	4	36.4	
Hospitalization										
Clinicians consideration	62	100.0	10***	21.74	**<0.001**	46	100.0	16	100.0	–
Patients hospitalized (nmiss = 1)	62	100.0	12	26.7	**<0.001**	46	100.0	16	100.0	–
Hospitalization (days) (mean ± SD, min-max)	32.5 ± 31.3	2–119	31.5 ± 29.9	1–78	0.743	33.3 ± 32.9	2–119	27.0 ± 15.4	12–53	**<0.001**
Department hospitalization										

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Table 1 (*continued*)

	ARLD					Subgroup invasive ARLD				
	Invasive		**Allergy**		**p-value***	**Acute**		**Chronic**		**p-value***
	IPA + CPA		**ABPA**			**IPA**		**CPA**		
	(n=62)		**(n=46)**			**(n=46)**		**(n=16)**		
	n	%	n	%		n	%	n	%	
Intensive Care Unit	31	50.0	0	0	**<0.001**	26	56.5	5	31.3	0.146
Emergency	1	1.6	2	4.4	0.574	0	0	1	6.3	0.258
Respiratory	17	27.4	10	21.7	0.654	8	17.4	9	56.3	**0.007**
Haematology	5	8.1	0	0	0.070	5	10.9	0	0	0.315
Transplantation	3	4.8	0	0	0.260	3	6.5	0	0	0.562
IHU Méditerranée Infection	3	4.8	0	0	0.260	2	4.4	1	6.3	1.000
Internal medicine	2	3.2	0	0	0.506	2	4.4	0	0	1.000
Respiratory consultation	0	0.0	34	73.9	**<0.001**	0	0	0	0	–
Treatment										
Treated patients (nmiss = 1)	60	96.8	10	21.7	**<0.001**	45	97.8	15	93.8	0.453
2nd line antifungal treatment (n)	23		43			17		6		
Yes	19	82.6	2	4.7	**<0.001**	13	76.5	6	100	0.539
Systemic corticosteroid	0	0.0	7	15.2	**0.002**	0	0	0	0	–
Outcome										
1 month fatality****	19	30.6	0	0	**<0.001**	19	42.2	0	0	**0.001**
3 months fatality (nmiss = 6)	23	39.0	0	0	**<0.001**	21	47.7	2	14.3	**0.049**
ABPA exacerbation in 12 months	NA	NA	6	13.0		–	–	–	–	

*Note: we used the Fisher's exact test for qualitative variables and the Mann-Whitney *U* test for quantitative variables; ** CPA *(A. tubingensis, A. flavus, and A. lentulus),* ABPA *(A. westerdijkiae, A. delacroxii, A. flavus, and A. oryzae);* ***10/46 patients with stable clinical conditions, 11/46 cystic fibrosis treated ETI, 8 patients treated CTC and biotherapy before diagnosis, 7/46 Uncontrolled asthma patients due to other factors; 18/29 cystic fibrosis patients not treated by ETI*;* ****1 IPA patient died before diagnosis.

NA: Not applicable. Significant results are in bold.

Among these, *A. fumigatus* was the predominant species in all ARLD patient groups. Other *Aspergillus* species were less frequently isolated in CPA patients, including *A. tubingensis*, *A. flavus* and *A. lentulus*. In ABPA patients, 10 (76.9 %) were positive for *A. fumigatus*, while less common species included *A. westerdijkiae*, *A. delacroxii*, *A. flavus* and *A. oryzae*.

3.5. Diagnostic and treatment

In the patients with invasive ARLD we observed complete (100 %) concordance between the official diagnostic criteria and the clinician's assessment. Consequently, 45 (97.8 %) IPA patients and 15 (93.8 %) CPA patients received treatment. In contrast, only 10 (21.7 %) of the patients with allergic ARLD were considered by the physician to have ABPA ($p < 0.001$). Of the 36 patients with discrepancies between clinical diagnosis and treatment recommendations, 10 (27.8 %) were clinically stable, 11 (30.6 %) had CF treated with elexacaftor/tezacaftor/ivacaftor (ETI) therapy and 8 (22.2 %) were treated with corticosteroids or biological therapies. The remaining 7 cases were patients with uncontrolled asthma due to other factors such as intolerance, poor adherence, presence of risk factors (e.g. smoking) or lack of maintenance therapy.

3.6. Outcome

The hospitalization rate for patients with IPA was 46 (100 %), with 26 (56.5 %) requiring admission to intensive care. One patient had incomplete treatment data and one patient died before a definitive diagnosis could be made. In total, 21 patients died within 3 months, giving a case-fatality rate of 47.7 %. Among CPA patients, 31.3 % were admitted to intensive care at the time of diagnosis and two patients (14.3 %) died within three months. None of the 46 ABPA patients died, but 6 (13 %) experienced an exacerbation within 12 months.

4. Discussion

We performed a retrospective analysis at the University Hospital of Marseille, France, over a two-year period to estimate the prevalence of the three main clinical presentations of ARLD: invasive pulmonary aspergillosis (IPA), chronic pulmonary aspergillosis (CPA) and allergic bronchopulmonary aspergillosis (ABPA). We diagnosed 46 cases of IPA, 16 cases of CPA and 46 cases of ABPA according to recommended criteria [8,13,14]. To our knowledge, this is the first comprehensive epidemiological study of all three forms of pulmonary aspergillosis conducted worldwide. Previous studies have typically focused on one or two forms of the disease [9–12].

We combined IPA and CPA patients into a single 'invasive' ARLD group due to the invasive nature, mortality and severity of these two diseases [25]. Similarly, ABPA was classified as 'allergic' ARLD due to its allergic characteristics. The mean age of patients with allergic ARLD was significantly younger (34.4 ± 20.6 years) than that of patients with invasive ARLD (53.24 ± 18.9 years). This may be explained by the demographic characteristics of ABPA patients [26]. A significant proportion (63.0 %) of the ABPA group consisted of patients with cystic fibrosis (CF-ABPA) - a disease caused by a genetic mutation in the CFTR gene that predominantly affects younger individuals [27,28]. Patients with invasive ARLD were significantly more likely to have cardiovascular disease than those with allergic ARLD ($p = 0.007$). These findings may be explained by the significantly younger age of patients with allergic ARLD compared to those with invasive ARLD and are consistent with previous reports in the literature [7,19,29,30].

Interestingly, our study showed that 15.2 % of IPA patients were receiving biotherapy (including 71.4 % receiving rituximab, 14.3 % receiving binutuzumab and 14.3 % receiving tocilizumab). Biotherapy may be a potential risk factor for invasive ARLD. These therapies have mainly been used to prevent graft rejection in lung transplant recipients or to treat cytokine storms in severe COVID-19 patients. Rituximab has been retained in the 2019 EORTC/MSG diagnostic criteria [19,31], while tocilizumab is an emerging potential risk factor that has been described in a limited number of case reports in patients with invasive ARLD [32,33]. Obinutuzumab, however, has no documented evidence of an association with IPA in the current literature. This highlights how the emergence of biotherapeutic molecules post-2020 is likely to impact on the management of IPA.

The diagnosis of ARLD in clinical practice remains challenging despite current diagnostic standards [5,7,14]. In our study, the rate of clinician diagnosis of invasive ARLD (both IPA and CPA) is largely

consistent with established diagnostic criteria, which may be explained by its invasive and life-threatening nature. Indeed, the high severity and mortality associated with IPA, often exceeding 40 %, require high clinician vigilance, especially in patients with known risk factors [12]. Similarly, in patients with CPA, early diagnosis and prompt treatment are important to prevent life-threatening haemoptysis [7]. Our study highlights the potential seriousness of CPA: 37.5 % of patients had haemoptysis, with one case of recurrent mild haemoptysis requiring hospital admission and two cases of massive haemoptysis leading to death despite medical intervention such as bronchial artery embolization or lung resection.

Conversely, we observed a discrepancy between ABPA cases diagnosed according to current diagnostic criteria [8,13] and those diagnosed and treated by clinicians. Indeed, of the 46 ABPA patients in our study, only 10 (21.7 %) were considered and treated by clinicians. This highlights the unique challenge of diagnosing ABPA. The evolving diagnostic criteria for ABPA, which have been updated three times in the last four years, and the late inclusion of specific clinical criteria, only since the 2024 ABPA guidelines, may lead to confusion among clinicians [8,13,14].

Of 36 patients with discrepancies between clinical diagnosis and treatment recommendations, 10 (27.8 %) were clinically stable. Clinicians must carefully weigh the potential benefits of long-term antifungal or corticosteroid therapy against the associated side effects, as immediate intervention is not always necessary [34,35]. Therefore, clinical criteria have been included in the recent ISHAM 2024 recommendations to guide treatment in clinical practice [14]. However, despite these advances, treatment guidelines remain inadequate, especially for CF patients treated with ETI therapy [26,34,35].

In fact, 11 (30.6 %) of the 36 ABPA patients not considered by clinicians were CF patients treated with ETI therapy. ETI therapy, which combines CFTR channel opening and channel correction, is an FDA-approved treatment for CF patients from two years of age [28,34]. CFTR modulators have been proposed to reduce ABPA exacerbations due to their disease-modifying effects on acquired CFTR dysfunction [35]. A recent 2025 study reported that during ETI treatment, pulmonary outcomes improved, *A. fumigatus* colonisation and sensitisation decreased, and no ABPA episodes were observed in people with CF with a clinical history of *A. fumigatus* colonisation [28,35]. In fact, lumacaftor/ivacaftor treatment has been shown to promote repair of damaged airway epithelial cells in CF by supporting epithelial function through surface hydration and pH regulation - key factors in maintaining epithelial barrier integrity and innate immune defence, particularly in the airways [36,37]. In addition, CFTR modulators alter cellular metabolism to help reduce the hyperinflammatory response characteristic of CF-ABPA [28,38], which may explain why these patients were not considered by clinicians in our study. In practice, it is not practical to combine ETI therapy and azoles due to drug interactions, with the azole reducing the clearance of the CFTR modulator ivacaftor [39].

A recent development in the treatment of acute ABPA and for maintenance therapy is the use of inhaled antifungals, which have fewer side effects than systemic medications and appear to be more suitable for children with CF or CF-ABPA patients on ETI therapy [14,28,39]. However, none of the patients in our study received inhaled antifungals and further studies are needed to prove their efficacy. The remaining 7 ABPA patients who were not considered by clinicians were from different clinical settings. Treatment decisions for patients with ABPA remain a significant challenge and require individualised management [40,41]. Key factors influencing treatment decisions include clinical severity, confounders of poorly controlled asthma, intolerance, adherence, long-term side effects of corticosteroids or antifungals, and drug-drug interactions [40,41]. For example, ABPA patients with asthma may not require specific treatment if current asthma treatments are adequate to control the disease [39]. Finally, our mortality data are similar to other French data with a 47.7 % IPA [9,12] and 14.3 % CPA three-month fatality rate, which is in line with global data [42]. The high ICU admission and mortality rates in our IPA patients likely reflect advanced disease and comorbidities typical of tertiary referral centres. Causes of death included ARDS (n = 23), septic shock, cardiac arrest, metastatic cancer, severe CAPA/IAPA, and graft rejection. Similarly, the high ICU admission rate (31.3 %) in our CPA patients is driven by the presence of severe underlying conditions and complications, such as haemoptysis, post-surgical air leaks, or malignancy, rather than CPA alone. Interestingly, despite this finding, the CPA-related mortality, 14.3 % (2/16) at both 3 and 12 months, falls within the range reported in previous studies (7–32 %) at 1 year [43]. Both deaths were due to severe haemoptysis that did not respond to therapeutic interventions.

Fortunately, no ABPA patient died during the two-year study, although 6 (13.0 %) patients had an exacerbation within 12 months of diagnosis. According to the literature, death is rare in ABPA patients, but exacerbations are common [4].

Aspergillus-related lung disease represents a complex clinical spectrum. As shown in Fig. 2, within 2 years we identified 17 patients with SAFS, 11 with AS, 6 with *Aspergillus* bronchitis, 19 with *Aspergillus* colonisation, and three simple aspergillomas. A few cases of overlap between ABPA and CPA have been reported in the literature worldwide [44,45]. ABPA-CPA overlap remains a rare entity, which is now included in the revised ISHAM-ABPA 2024 guidelines although its definition remains unclear [14]. It combines clinical, radiological, and immunological features posing diagnostic and therapeutic challenges. However, we observed no such cases during the limited study period (2022–2023).

4.1. Limitation

Our study was limited by the retrospective nature of the data collection, particularly the data on patient treatment (drugs and correct duration). In addition, the monocentric study design inherently limits the generalizability of our results, which cannot be extrapolated to other patient populations. Patient selection in our study was based on the presence of specific serological markers: galactomannan antigen, *Aspergillus*-specific IgG and *Aspergillus*-specific IgE, which were requested at the discretion of the treating physicians. Testing was not standardized and depended on clinical suspicion, so we were unable to document the specific clinical contexts that led to testing, particularly in patients without available data. Additionally, we did not collect information on patients with negative results or on those who were not tested, which may limit the generalizability of our findings. However, these serologies allowed us to identify 11 cases of *Aspergillus* sensitisation and 17 cases of severe asthma with fungal sensitisation. However, it is important to note that the true prevalence of *Aspergillus* colonisation in our study population may have been underestimated due to our study design, which did not rely on respiratory culture screening.

5. Conclusions

Our two-year study shows the true prevalence and significant 3-month fatality rates associated with IPA and CPA at the University Hospitals of Marseille. We would like to highlight two notable points: the observation that biotherapies are a potential new risk factor for invasive ARLD, and the inconsistencies in the diagnosis of ABPA. The first requires further studies to confirm and quantify the effect of biotherapies on invasive ARLD. The second highlights the urgent need to improve diagnostic algorithms to better reflect actual clinical practice.

CRediT authorship contribution statement

Thi Quynh Pham: Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Léa Delorme:** Writing – review & editing, Formal analysis. **Sébastien Cortaredona:** Writing – review & editing, Methodology, Formal analysis. **Stéphane Ranque:** Writing – review & editing, Writing – original draft, Validation, Supervision, Methodology,

Conceptualization. **Estelle Menu:** Writing – review & editing, Writing – original draft, Validation, Supervision, Methodology, Data curation, Conceptualization.

Transparency declaration

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.rmed.2025.108206.

References

[1] J.A. Sugui, K.J. Kwon-Chung, P.R. Juvvadi, J.-P. Latgé, W.J. Steinbach, *Aspergillus fumigatus* and related species, Cold Spring Harb. Perspect. Med. 5 (2014) a019786, https://doi.org/10.1101/cshperspect.a019786.

[2] J.P. Latgé, *Aspergillus fumigatus* and aspergillosis, Clin. Microbiol. Rev. 12 (1999) 310–350, https://doi.org/10.1128/CMR.12.2.310.

[3] S. Gago, D.W. Denning, P. Bowyer, Pathophysiological aspects of *Aspergillus* colonization in disease, Med. Mycol. 57 (2019) S219–S227, https://doi.org/10.1093/mmy/myy076.

[4] M.L. Chabi, A. Goracci, N. Roche, A. Paugam, A. Lupo, M.P. Revel, Pulmonary aspergillosis, Diagn. Interv. Imag. 96 (2015) 435–442, https://doi.org/10.1016/j.diii.2015.01.005.

[5] P. Koehler, M. Bassetti, A. Chakrabarti, S.C.A. Chen, A.L. Colombo, M. Hoenigl, et al., Defining and managing COVID-19-associated pulmonary aspergillosis: the 2020 ECMM/ISHAM consensus criteria for research and clinical guidance, Lancet Infect. Dis. 21 (2021) e149–e162, https://doi.org/10.1016/S1473-3099(20)30847-1.

[6] P.E. Verweij, B.J.A. Rijnders, R.J.M. Brüggemann, E. Azoulay, M. Bassetti, S. Blot, et al., Review of influenza-associated pulmonary aspergillosis in ICU patients and proposal for a case definition: an expert opinion, Intensive Care Med. 46 (2020) 1524–1535, https://doi.org/10.1007/s00134-020-06091-6.

[7] T.F. Patterson, G.R. Thompson, D.W. Denning, J.A. Fishman, S. Hadley, R. Herbrecht, et al., Practice guidelines for the diagnosis and management of aspergillosis: 2016 update by the infectious diseases society of America, Clin. Infect. Dis. 63 (2016) e1–e60, https://doi.org/10.1093/cid/ciw326.

[8] R. Agarwal, I.S. Sehgal, S. Dhooria, V. Muthu, K.T. Prasad, A. Bal, et al., Allergic bronchopulmonary aspergillosis, Indian J. Med. Res. 151 (2020) 529–549, https://doi.org/10.4103/ijmr.IJMR_1187_19.

[9] F. Bongomin, S. Gago, R. Oladele, D. Denning, Global and multi-national prevalence of fungal diseases—estimate precision, J. Fungi. 3 (2017) 57, https://doi.org/10.3390/jof3040057.

[10] T. Maitre, J. Cottenet, C. Godet, A. Roussot, N. Abdoul Carime, V. Ok, et al., Chronic pulmonary aspergillosis: prevalence, favouring pulmonary diseases and prognosis, Eur. Respir. J. 58 (2021) 2003345, https://doi.org/10.1183/13993003.03345-2020.

[11] J.-P. Gangneux, M.-E. Bougnoux, C. Hennequin, C. Godet, J. Chandenier, D. W. Denning, et al., An estimation of burden of serious fungal infections in France, J. Mycol. Medicale. 26 (2016) 385–390, https://doi.org/10.1016/j.mycmed.2016.11.001.

[12] S. Bretagne, K. Sitbon, M. Desnos-Ollivier, D. Garcia-Hermoso, V. Letscher-Bru, S. Cassaing, et al., Active surveillance program to increase awareness on invasive fungal diseases: the French RESSIF network (2012 to 2018), mBio 13 (2022) e0092022, https://doi.org/10.1128/mbio.00920-22.

[13] K. Asano, A. Hebisawa, T. Ishiguro, N. Takayanagi, Y. Nakamura, J. Suzuki, et al., New clinical diagnostic criteria for allergic bronchopulmonary aspergillosis/mycosis and its validation, J. Allergy Clin. Immunol. 147 (2021) 1261–1268.e5, https://doi.org/10.1016/j.jaci.2020.08.029.

[14] R. Agarwal, I.S. Sehgal, V. Muthu, D.W. Denning, A. Chakrabarti, K. Soundappan, et al., Revised ISHAM-ABPA working group clinical practice guidelines for diagnosing, classifying and treating allergic bronchopulmonary aspergillosis/mycoses, Eur. Respir. J. 63 (2024) 2400061, https://doi.org/10.1183/13993003.00061-2024.

[15] M. Cornet, L. Fleury, C. Maslo, J.-F. Bernard, G. Brücker, Invasive Aspergillosis Surveillance Network of the Assistance Publique-Hôpitaux de Paris. Epidemiology of invasive aspergillosis in France: a six-year multicentric survey in the Greater Paris area, J. Hosp. Infect. 51 (2002) 288–296, https://doi.org/10.1053/jhin.2002.1258.

[16] C.-W. Hsiao, T.-H. Yen, Y.-C. Wu, J.-P. Chen, Y.-Y. Chen, W.-N. Huang, et al., Comparison of *Aspergillus*-specific antibody cut-offs for the diagnosis of aspergillosis, Front. Microbiol. 13 (2022) 1060727, https://doi.org/10.3389/fmicb.2022.1060727.

[17] Marseille Climate, Weather By Month, Average Temperature (France) - Weather Spark n.d. https://weatherspark.com/y/51593/Average-Weather-in-Marseille-France-Year-Round (accessed July 20, 2024).

[18] Organisation-aphm-chiffre-cles (2022) Présentation de l'AP-HM | AP-HM. https://fr.ap-hm.fr/nous-connaitre. Accessed 10 Jun 2025.

[19] J.P. Donnelly, S.C. Chen, C.A. Kauffman, W.J. Steinbach, J.W. Baddley, P. E. Verweij, et al., Revision and update of the consensus definitions of invasive fungal disease from the European organization for research and treatment of cancer and the mycoses study group education and research consortium, Clin. Infect. Dis. 71 (2020) 1367–1376, https://doi.org/10.1093/cid/ciz1008.

[20] R. Agarwal, A. Khan, M. Garg, A.N. Aggarwal, D. Gupta, Chest radiographic and computed tomographic manifestations in allergic bronchopulmonary aspergillosis, World J. Radiol. 4 (2012) 141–150, https://doi.org/10.4329/wjr.v4.i4.141.

[21] R. Agarwal, V. Muthu Fccp, A. Aggarwal, Exacerbation in allergic bronchopulmonary aspergillosis: identification of risk factors and developing a prediction model, Chest (Am. Coll. Chest Physicians) (2019) A1037, https://doi.org/10.1016/j.chest.2019.08.957.

[22] A. Kanj, N. Abdallah, A.O. Soubani, The spectrum of pulmonary aspergillosis, Respir. Med. 141 (2018) 121–131, https://doi.org/10.1016/j.rmed.2018.06.029.

[23] C. Kosmidis, D.W. Denning, The clinical spectrum of pulmonary aspergillosis, Thorax 70 (2015) 270–277, https://doi.org/10.1136/thoraxjnl-2014-206291.

[24] M.-L. Luong, C. Chaparro, A. Stephenson, C. Rotstein, L.G. Singer, V. Waters, et al., Pretransplant *Aspergillus* colonization of cystic fibrosis patients and the incidence of post-lung transplant invasive aspergillosis, Transplantation 97 (2014) 351–357, https://doi.org/10.1097/01.TP.0000437434.42851.d4.

[25] D.W. Denning, Global incidence and mortality of severe fungal disease, Lancet Infect. Dis. 24 (2024) e428–e438, https://doi.org/10.1016/S1473-3099(23)00692-8.

[26] V. Muthu, I.S. Sehgal, K.T. Prasad, S. Dhooria, M. Garg, A.N. Aggarwal, et al., Epidemiology and outcomes of allergic bronchopulmonary aspergillosis in the elderly, Mycoses (Berl.) 65 (2022) 71–78, https://doi.org/10.1111/myc.13388.

[27] D.A. Stevens, R.B. Moss, V.P. Kurup, A.P. Knutsen, P. Greenberger, M.A. Judson, et al., Allergic bronchopulmonary aspergillosis in cystic fibrosis–state of the art: cystic fibrosis foundation consensus conference, Clin. Infect. Dis. Off. Publ. Infect. Dis. Soc. Am. 37 (Suppl 3) (2003) S225–S264, https://doi.org/10.1086/376525.

[28] P. Chatterjee, C.T. Moss, S. Omar, E. Dhillon, C.D. Hernandez Borges, A.C. Tang, et al., Allergic bronchopulmonary aspergillosis (ABPA) in the era of cystic fibrosis transmembrane conductance regulator (CFTR) modulators, J. Fungi Basel. Switz. 10 (2024) 656, https://doi.org/10.3390/jof10090656.

[29] I.W. Yerbanga, S. Nakanabo Diallo, T. Rouamba, O. Denis, H. Rodriguez-Villalobos, I. Montesinos, et al., A systematic review of epidemiology, risk factors, diagnosis, antifungal resistance, and management of invasive aspergillosis in Africa, J. Mycol. Medicale. 33 (2023) 101328, https://doi.org/10.1016/j.mycmed.2022.101328.

[30] B. Yang, T. Kim, J. Ryu, H.Y. Park, B. Hwangbo, S.-Y. Kong, et al., Increased incidence and associated risk factors of aspergillosis in patients with bronchiectasis, J. Personalized Med. 11 (2021) 422, https://doi.org/10.3390/jpm11050422.

[31] L. Gil, M. Kozlowska-Skrzypczak, A. Mol, D. Poplawski, J. Styczynski, M. Komarnicki, Increased risk for invasive aspergillosis in patients with lymphoproliferative diseases after autologous hematopoietic SCT, Bone Marrow Transplant. 43 (2009) 121–126, https://doi.org/10.1038/bmt.2008.303.

[32] K.-L. Wu, C.-Y. Chang, H.-Y. Sung, T.-Y. Hu, L.-K. Kuo, Association of tocilizumab and invasive aspergillosis in critically ill patients with severe COVID-19 pneumonia and acute respiratory distress syndrome, J. Fungi Basel. Switz. 8 (2022) 339, https://doi.org/10.3390/jof8040339.

[33] V. Gidwani, S. Chauhan, Pulmonary Aspergillosis post-tocilizumab treatment in a patient with COVID-19 pneumonia, Chest (Am. Coll. Chest Physicians) 162 (2022) A384, https://doi.org/10.1016/j.chest.2022.08.296.

[34] Commissioner O of the, FDA Approves New Breakthrough Therapy for Cystic Fibrosis, FDA, 2020. https://www.fda.gov/news-events/press-announcements/fda-approves-new-breakthrough-therapy-cystic-fibrosis. (Accessed 30 January 2025).

[35] C. Lanfranchi, G. Alicandro, L. Cariani, B.S. Orena, A. Gramegna, C. Rizza, et al., Respiratory outcomes and *Aspergillus* serology following elexacaftor/tezacaftor/ivacaftor therapy in people with cystic fibrosis and a history of *Aspergillus fumigatus* infection, Lung (N. Y.) 203 (2025) 24, https://doi.org/10.1007/s00408-024-00781-4.

[36] S.D. Patel, T.R. Bono, S.M. Rowe, G.M. Solomon, CFTR targeted therapies: recent advances in cystic fibrosis and possibilities in other diseases of the airways, Eur. Respir. Rev. Off. J. Eur. Respir. Soc. 29 (2020) 190068, https://doi.org/10.1183/16000617.0068-2019.

[37] D. Adam, C. Bilodeau, L. Sognigbé, É. Maillé, M. Ruffin, E. Brochiero, CFTR rescue with VX-809 and VX-770 favors the repair of primary airway epithelial cell cultures from patients with class II mutations in the presence of Pseudomonas aeruginosa exoproducts, J. Cyst. Fibros. 17 (2018) 705–714, https://doi.org/10.1016/j.jcf.2018.03.010.

[38] L.J. Caverly, S.A. Riquelme, K.B. Hisert, The impact of highly effective modulator therapy on cystic fibrosis Microbiology and inflammation, Clin. Chest Med. 43 (2022) 647–665, https://doi.org/10.1016/j.ccm.2022.06.007.
[39] R.B. Moss, Correction: moss, R.B. Severe fungal asthma: a role for biologics and inhaled antifungals. J. Fungi 2023, 9, 85, J. Fungi Basel. Switz. 9 (2023) 450, https://doi.org/10.3390/jof9040450.
[40] A.S. Moreira, D. Silva, A.R. Ferreira, L. Delgado, Antifungal treatment in allergic bronchopulmonary aspergillosis with and without cystic fibrosis: a systematic review, Clin. Exp. Allergy J. Br. Soc. Allergy Clin. Immunol. 44 (2014) 1210–1227, https://doi.org/10.1111/cea.12333.
[41] C. Chenivesse, A.-L. Brun, J. Cadranel, E. Fréalle, F. Laurent, J. Vitte, Respifil Pnds Abpa Définitif, 10 19, 2021, p. 2021.
[42] A. Sengupta, A. Ray, A.D. Upadhyay, K. Izumikawa, M. Tashiro, Y. Kimura, et al., Mortality in chronic pulmonary aspergillosis: a systematic review and individual patient data meta-analysis, Lancet Infect. Dis. S1473–3099 (24) (2024), https://doi.org/10.1016/S1473-3099(24)00567-X, 00567-X.
[43] Y. Kimura, Y. Sasaki, J. Suzuki, J. Suzuki, H. Igei, M. Suzukawa, H. Matsui, Prognostic factors of chronic pulmonary aspergillosis: a retrospective cohort of 264 patients from Japan, PLoS One 16 (2021) e0249455, https://doi.org/10.1371/journal.pone.0249455.
[44] Y. Tsukamoto, Y. Ito, Y. Obase, T. Takazono, N. Nakada, N. Ashizawa, T. Hirayama, K. Takeda, S. Ide, N. Iwanaga, M. Tashiro, N. Hosogaya, S. Fukahori, C. Fukushima, K. Yanagihara, K. Izumikawa, H. Mukae, Serum cytokine changes in a patient with chronic pulmonary aspergillosis overlapping with allergic bronchopulmonary aspergillosis, Intern. Med. 63 (2024) 1659–1664, https://doi.org/10.2169/internalmedicine.2234-23.
[45] D. Lowes, L. Chishimba, M. Greaves, D.W. Denning, Development of chronic pulmonary aspergillosis in adult asthmatics with ABPA, Respir. Med. 109 (2015) 1509–1515, https://doi.org/10.1016/j.rmed.2015.09.007.