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Clinical outcomes of patients with respiratory azole-resistant Aspergillus fumigatus in Barcelona, Spain

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Abstract

Objective

To determine the prevalence of azole-resistant *A. fumigatus* (ARAF) respiratory isolates and its clinical relevance.

Methods

Retrospective, single-center study of adult patients with ≥ 1 respiratory ARAF isolate (resistance to ≥ 1 triazole according to EUCAST) between May 2022 and December 2024. The primary outcome was the rate of ARAF among all *A. fumigatus sensu stricto* (ss) isolates. The prevalence of aspergillosis and 90-day mortality were assessed as secondary endpoints.

Results

Among 476 patients with *A. fumigatus* ss isolates, ARAF was identified in 75 (16%); 66 had available clinical data to be finally included. Compared to colonized individuals (n = 56, 85%), patients with aspergillosis (n = 10, 15%) were more frequently immunosuppressed (8/56 vs 6/10, p < 0.01). Six patients had invasive aspergillosis (IA), 3 of whom received azole-based inadequate empirical treatment. Forty-five (68%) patients had a pan-azole resistant phenotype but only 14 (21%) had prior antifungal exposure. Overall, the 90-day attributable mortality was 6%. Among patients with fungal disease, 90-day attributable mortality reached 40%, increasing to 67% in IA.

Conclusions

In our setting, the prevalence of ARAF was high and mainly reflected colonization. Invasive disease was uncommon but associated high mortality rates. Active empirical therapy against ARAF should be considered in high-risk patients with invasive aspergillosis until azole-resistance is excluded.

INTRODUCTION

Over the last two decades, the epidemiology of *Aspergillus fumigatus* has been reshaped by the emergence and spread of azole-resistant strains (ARAF). First described in Europe and the US, the prevalence of ARAF has increased worldwide [1–5] with a heterogeneous distribution across studies, including both clinical and environmental isolates [6–8]. Recent epidemiological reports in Europe have pointed the Netherlands as one of the areas with highest ARAF rates, which can reach 16%, with an increasing trend overtime [9].

In Spain, early studies conducted by Alastruey et al.[10] showed that azole resistance in *A. fumigatus* among clinical samples was largely restricted to cryptic species, with a single case detected in *sensu stricto* (ss) isolates. Updated surveillance analyses from the same group, however, reported three cases of azole-resistant *A. fumigatus* ss in 439 clinical samples [11]. Thereafter, a trend towards an increased prevalence has been noted in the last ten years, with the ASPEIN study reporting a concerning global prevalence of 5.5% among isolates collected in 2019 from several Spanish hospitals distributed nationwide [12]. Globally, the TR34/L98H cyp51A mutation has been consistently identified as the predominant resistance mechanism in several clinical and epidemiological studies conducted both in Spain and across Europe [13–15]. It should be noted, however, that a key limitation of these surveillance studies is the inclusion of heterogeneous populations and the lack of assessment of the clinical relevance of ARAF isolates, with most failing to differentiate colonization from true infection [16–18]. This distinction is particularly important because azoles remain the recommended first-line treatment of aspergillosis [19, 20], with a potential increase of inadequate empirical antifungal treatment in high-prevalent settings and ultimately increase mortality rates [21–24]. Considering that first-line non-azole antifungal strategies have been suggested in settings where resistance rates exceed 10% [20, 25, 26], a proper knowledge of the local epidemiology emerges as a critical issue to initiate an early and adequate antifungal therapy to improve outcomes.

Thus, in order to accurately define the true impact of ARAF isolates, it is crucial to integrate microbiological findings with clinical data to facilitate tailored antifungal therapy [27–29]. The aim of this study was to determine the prevalence of azole resistance among clinical isolates of *A. fumigatus* ss in our center, as well as its clinical impact and associated mortality

METHODS

Study design and setting

This was a single-centre, retrospective observational study conducted from May 2022 to December 2024 at Vall Hebron Barcelona Hospital Campus, a 1000-bed referral centre in Barcelona, Spain.

Participants

All adult (≥ 18 years) patients with at least one *Aspergillus fumigatus* ss isolate obtained from a respiratory sample during the study period were eligible for the study. Among them, only those in whom an azole-resistant *A. fumigatus* ss (≥ 1 triazole resistance according to EUCAST breakpoints) isolate was identified were included in the final analysis. The exclusion criteria were: (1) unavailability of key data related to clinical features and mortality, (2) death within the first 48 hours after sample collection, (3) non-*fumigatus* Aspergilli within the *sectio fumigati* or other *Aspergillus* species (spp.) (4) patients with ARAF and a simultaneous azole-susceptible *A. fumigatus* or other *Aspergillus* spp. isolate within the same clinical episode. The follow-up period was 3 months from the ARAF isolate collection.

Data collection and variables

Patients were identified through microbiological records and codified into a password-protected database hosted in RedCap (Research Electronic Data Capture hosted at Vall d'Hebron Institute of Research). Data regarding clinical and microbiological characteristics, and outcomes were collected. Demographic and clinical variables were analyzed, including predisposing factors for fungal infection, such as prior immunosuppressive therapies (within the 60 days prior to ARAF isolation), hematological malignancy (HM), prior hematopoietic stem cell transplant (HSCT) or solid organ transplant (SOT), intensive care unit (ICU) admission or prior antifungal exposure including antifungal prophylaxis (within 30 days prior to ARAF isolation).

Definitions

A clinical episode was defined as the isolation of ARAF associated with acute respiratory symptoms or, in case of chronic respiratory disease, when ARAF identification coincided with an exacerbation of their baseline respiratory symptoms. Invasive aspergillosis (IA) was classified according to the updated 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 (EORTC-MSRC 2020)[30] or according to FUNDICU criteria in case of critically ill patients [31]. In case of respiratory viral co-infection or chronic obstructive pulmonary disease (COPD) comorbidity other accepted criteria were used [32–34]. Chronic pulmonary aspergillosis (CPA) and allergic bronchopulmonary aspergillosis (ABPA) were defined according to previously reported definitions [35, 36]. Breakthrough invasive pulmonary aspergillosis (bIPA) was defined as that occurring during exposure to antifungals, which in the case of isavuconazole and liposomal amphotericin B (L-Amb) was defined as a minimum of 7-day period, according to previous consensus [37, 38]. ARAF isolates in asymptomatic patients or in patients with chronic lung disease with unchanged baseline clinical status and no antifungal treatment were considered colonizers of the respiratory tract. Each case was individually reviewed by a multidisciplinary team of infectious disease and mycology experts.

Prior immunosuppressive regimens were classified as conventional chemotherapy (CT), targeted therapies (checkpoint inhibitors, monoclonal antibodies, BCL-2 and FLT3 inhibitors), calcineurin inhibitors or disease-modifying anti-rheumatic drugs (DMARDs) and corticosteroids (≥ 0.3 mg/kg prednisolone equivalent for ≥ 3 weeks in the preceding 60 days of ARAF isolate). Neutropenia was defined as an absolute neutrophile count (ANC) lower than 500/μL.

Antifungal treatment initiated at the time of fungal disease suspicion was considered empirical therapy. An inadequate empirical antifungal therapy (IAET) was considered when the patient did not receive an active antifungal agent before definite microbiological results.

Microbiological samples and antifungal susceptibility testing

A. fumigatus ss isolates were identified by their morphological traits and MALDI-TOFF and screened for azole resistance by using e-test strips (Liofilchem, Italy, and BioMerieux, France) as previously described [39]. Identification and azole resistance were confirmed at the Spanish National Reference Centre for Microbiology. To assess antifungal susceptibility, minimal inhibitory concentrations (MIC) to amphotericin B, itraconazole, voriconazole, posaconazole (Sigma-Aldrich, Madrid, Spain) and isavuconazole (Basilea Pharmaceutica International Ltd, Basel, Switzerland) were tested following the EUCAST EDef 9.3.2 procedure and using tissue-treated trays (CELLSTAR® Ref. 655 180, Greiner bio-one, Frickenhausen, Germany) and interpreted to updated EUCAST breakpoints [39]. *A. fumigatus* ss isolates with resistance to ≥ 1 triazole were classified as ARAF. The area of technical uncertainty (ATU) for the four azoles was defined in the updated breakpoints [40]. Interpretation of MICs falling in the ATU was done as follows: itraconazole and voriconazole (always considered resistant), posaconazole (considered resistant only if the isolate was also itraconazole resistant), isavuconazole (considered resistant only if the isolate was also voriconazole resistant).

Underlying mechanism of ARAF resistance was investigated by Cyp51A sequencing, as previously described [41].

Outcomes

The primary outcome was the rate of ARAF among *A. fumigatus* ss respiratory isolates. The prevalence of associated aspergillosis and early (30-day) and late (90-day) all-cause and attributable mortality were assessed as secondary endpoints. Clinical response to antifungal therapy was specifically analyzed in patients with fungal disease at 6 and 12 weeks after diagnosis.

Statistical methods

Categorical variables were expressed in absolute numbers and percentages, while quantitative variables were reported as medians and interquartile ranges (IQRs). Quantitative variables were compared using Mann-Whitney test and categorical variables with Fisher exact test or Chi-square test as appropriate. The prevalence of aspergillosis was calculated as the number of cases among the included patients. For the different available antifungals minimum inhibitory concentration (MICs) at percentile 50 and 90 and interquartile range were calculated. All-cause and attributable mortality were assessed at 30-day and 90-day follow-up in the overall cohort and across different clinical forms. A p value < 0.05 was considered significant. Statistical analyses were performed using IBM SPSS Statistics for Windows, Version 25.0(Armonk, NY: IBM Corp. 2017) and RStudio for Mac Version 2026.01.0 + 392 (Posit Software, PBC).

Ethics

The study was approved by the Institutional Review Board of Vall d'Hebron University Hospital (protocol number PR(AG)576/2025). It was conducted according to the Declaration of Helsinki guidelines. The

need for informed consent was waived by the Clinical Research Ethics Committee due to the retrospective design. The study results are reported following the STROBE recommendations (Table S1) [42].

RESULTS

Among 476 eligible patients with a culture positive for *A. fumigatus* ss during the study period, 75 (16%) were classified as ARAF. Of these, nine patients were excluded due to absence of relevant clinical data (n = 2), death within first 48 hours of ARAF isolation (n = 2) or concomitant isolation of an azole-susceptible *A. fumigatus* ss (n = 5), with a final cohort of 66 included patients (Fig. 1). Among them, we identified 111 ARAF isolates, with a median of 1 (IQR 1–1) isolate per patient. Fifty patients (50/66, 76%) had a single ARAF isolate while 16 had > 1 isolate (24%).

Most isolates were obtained through sputum samples (91/111, 82%), followed by bronchial aspirate (9/111, 8%), bronchoalveolar lavage (5/111, 4%), tracheal aspirates (4/111, 4%), and lung biopsy (2/111, 2%) samples.

Overall, 19 (29%) patients with a culture-positive ARAF had a previous *Aspergillus* spp. isolate identification and 14 (21%) had been previously exposed to antifungals, mainly used as prophylaxis in the setting of HM or lung transplant. Of these, most patients (11/14, 79%) received mould-active short-chain azoles, mainly isavuconazole (6/11, 56%).

When analysing azole-resistance patterns, resistance to itraconazole, voriconazole, isavuconazole, and posaconazole was identified in 105 (95%), 83 (75%), 64 (58%) and 58 (52%) isolates respectively. According to EUCAST clinical breakpoints, a pan-triazole resistant phenotype was present in 52 (47%) of the 111 isolates from 45 (68%) of all included patients. Median MICs for different antifungal agents are shown in Table 1.

Table 1
In vitro susceptibilities of the 114 azole-resistant *Aspergillus fumigatus sensu stricto* isolates

Antifungal	MIC interquartile range	MIC 50	MIC 90
Liposomal Amphotericin B*	0.25–0.5	0.38	1.0
Voriconazole	0.5–2	1.0	3
Isavuconazole‡	1–2	1.5	3
Itraconazole	4–6	6.0	8
Posaconazole‡	0.38–0.5	0.5	1
Anidulafungin*	0.032–0.047	0.047	0.064
Caspofungin‡	0.003–0.008	0.006	0.008
Micafungin‡	0.003–0.005	0.003	0.008

Abbreviations: MIC, minimum inhibitory concentration;

* MICs for amphotericin B and anidulafungin were available for 75/114 isolates; ‡ MICs for isavuconazole, posaconazole, caspofungin, and micafungin were available for 74/114 isolates

Among the 83 voriconazole-resistant isolates, 64 were also resistant to isavuconazole and one was isavuconazole-susceptible. In the remaining 18 isolates, isavuconazole susceptibility was not tested.

Cyp51A sequencing was performed on 20 isolates obtained from 20 different patients. Mutations were identified in 90% of them (18/20). The most frequently detected mutation was TR34 (17/18, 94%), with a single isolate (1/18, 6%) carrying a TR46 mutation. Among isolates with Cyp51A mutations, 89% (16/18) exhibited a pan-azole-resistant phenotype.

Ten (15%) patients were diagnosed with azole-resistant aspergillosis and the remaining 56 (85%) were considered colonized (Fig. 1). Neither of the colonized patients received antifungals nor developed aspergillosis during follow-up. As compared to colonized patients, individuals with azole-resistant aspergillosis were more frequently immunosuppressed (8/56 vs 6/10, $p < 0.01$), due to haematological malignancy or as solid organ recipients. Conversely, COPD and bronchiectasis were the main underlying factors in colonized individuals. Seventeen patients (26%) were under systemic corticosteroids at the time of ARAF isolation, 11 in combination with immunosuppressive therapy, with a similar distribution between groups. Prior or concomitant respiratory viral infections and CMV viremia tended to be more frequently reported in patients with aspergillosis. Only 3 patients (5%) presented neutropenia within the previous 30 days from ARAF isolation (median of 21 days, IQR 14.5–27.5), and all three were diagnosed of IA. The remaining baseline characteristics were similar across cohorts (Table 2).

Table 2
Baseline characteristics of included patients

Male gender	**Total (n = 66)**	**Colonized (n = 56)**	**Disease (n = 10)**	**p-value**
	43 (65)	**38 (68)**	**5 (50)**	**0.30**
Age	66 ± 16	68 ± 11	67 ± 9	0.89
Comorbidities	64 (97)	54 (96)	10 (100)	1.00
Structural lung disease	50 (76)	45 (80)	5 (50)	0.05
Bronchiectasis	26 (39)	22 (39)	4 (40)	
COPD	32 (49)	30 (54)	2 (20)	
Asthma	7 (11)	6 (11)	1 (10)	
Cystic fibrosis	5 (8)	3 (5)	2 (20)	
Interstitial lung disease	3 (5)	3 (5)	0	
Previous pulmonary tuberculosis	4 (6)	4 (7)	0	
Previous NMTB	1 (2)	0	1 (10)	
Solid organ malignancy	14 (21)	13 (23)	1 (10)	0.68
Lung neoplasm	8 (12)	8 (14)	0	
Hematological malignancy	8 (12)	5 (9)	3 (30)	0.10
HSCT	3 (5)	1 (2)	2 (20)	0.06
Bispecific antibodies	1 (2)	1 (2)	0	1.00
CAR-T therapy	1 (2)	0	1 (10)	0.15
Solid organ transplant	6 (9)	3 (5)	3 (30)	0.04
Lung	5 (8)	3 (5)	2 (20)	0.16
Respiratory viral co-infection	18 (27)	14 (25)	4 (40)	0.44
Systemic CMV co-infection	7 (11)	4 (7)	3 (30)	0.07
Other comorbidities	19 (29)	17 (30)	2 (20)	0.71
Diabetes Mellitus	6 (9)	6 (11)	0	0.58
Autoimmune disorders	6 (9)	5 (9)	1 (10)	1.00
Chronic kidney disease	2 (3)	2 (4)	0	1.00

Abbreviations: ARAF, azole-resistant *Aspergillus fumigatus*; spp., species; IA, invasive aspergillosis; CPA, chronic pulmonary aspergillosis; ABPA, allergic bronchopulmonary aspergillosis.

Male gender	Total (n = 66)	Colonized (n = 56)	Disease (n = 10)	p-value
	43 (65)	**38 (68)**	**5 (50)**	**0.30**
Primary immunodeficiency Chronic liver disease	1 (1)	1 (2)	0	1.00
Systemic corticosteroid use[1]	17 (26)	12 (21)	5 (50)	0.11
Inhaled corticosteroid use	38 (58)	32 (57)	6 (60)	1.00
Conventional chemotherapy	6 (9)	4 (7)	2 (20)	0.22
Targeted therapies[2]	10 (15)	8 (14)	2 (20)	0.65
Calcineurin inhibitors or DMARDs	8 (12)	4 (7)	4 (40)	0.02
Previous neutropenia[3]	3 (5)	0	3 (30)	< 0.01

Abbreviations: COPD, chronic obstructive pulmonary disease; NTMB, non-tuberculous mycobacteria; HSCT, hematopoietic stem cell transplant; CAR-T, Chimeric Antigen Receptor T-cell; CT, chemotherapy; CMV, cytomegalovirus; DMARDs, disease-modifying anti-rheumatic drugs; ICU, intensive care unit.

1. Defined as ≥ 0.3 mg/kg prednisolone equivalent for ≥ 3 weeks in the preceding 60 days of IA diagnosis; 2. Targeted therapies include: checkpoint inhibitors, monoclonal antibodies, immunotherapies, Venetoclax, FLT3 inhibitors; 3. Neutropenia was defined as an ANC < 500/µL in the preceding 30 days;

Abbreviations: ARAF, azole-resistant *Aspergillus fumigatus*; spp., species; IA, invasive aspergillosis; CPA, chronic pulmonary aspergillosis; ABPA, allergic bronchopulmonary aspergillosis.

Among the 10 patients who were diagnosed with azole-resistant aspergillosis, 6 met criteria for IA (4 invasive pulmonary aspergillosis [IPA], 1 ulcerative tracheobronchitis, and 1 subacute IPA), 3 for CPA, and 1 for ABPA. All patients with IA were receiving immunosuppressive therapy, either in the setting of active HM (3/6) or as SOT recipients (3/6). Four patients developed a virus-associated IA, mainly in the setting of a COVID confection (CAPA) (3/4). Chronic lung disease was present in all CPA cases; two had cystic fibrosis, while the remaining patient had a residual lung cavity following prior non-tuberculous mycobacterial infection.

Four patients were classified as having a bIPA. Of these, 2 of them under isavuconazole prophylaxis due to prolonged and profound neutropenia in the setting of HM. Therapeutic drug monitoring was not performed at the time of diagnosis.

All 6 patients with IA underwent empirical antifungal treatment, 3 patients received IEAT (50%) based on isavuconazole, upon disease suspicion. The median time between empirical treatment initiation to availability of antifungal sensibility testing was 10 days (IQR 6–13). In patients who initially received IEAT, the median delay from clinical suspicion to active antifungal treatment initiation was 12 days (IQR

6–14). None of the CPA or ABPA patients received antifungal therapy as the *Aspergillus* infection was not suspected. Overall, 30-and 90-day all-cause mortality were 3% (1/66) and 14% (9/66), respectively, with four (6%) deaths attributable to aspergillosis. In patients with fungal disease, all-cause and attributable mortality were similar at both 30 (10% [1/10]) and 90 days (40% [4/10]) from ARAF diagnosis. When focusing on patients with IA, the same pattern was observed, with all-cause and attributable mortality of 17% (1/6) at 30 days and 67% (4/6) at 90 days. In the same group, no differences in 90-day all-cause or attributable mortality rates were observed between patients who received adequate empirical antifungal therapy (2/3 [67%]) and those who received IEAT (2/3 [67%]). None of the patients diagnosed with CPA or ABPA died during the study period.

DISCUSSION

In our center, isolation of ARAF is a relatively frequent event, reaching 15.8% of patients with a clinically isolated *A. fumigatus* ss strain. To our knowledge, this is the first study to systematically assess the clinical impact of culture-positive ARAF patients in Spain, highlighting the following key points: 1) most ARAF isolates were identified in non-immunosuppressed individuals with no associated pathology; 2) ARAF-related invasive fungal disease was infrequent within the global population, mainly diagnosed in highly immunosuppressed patients who were inadequately treated with azoles.

In contrast to our data, early surveillance studies conducted in Spain reported very low rates of azole-resistant *A. fumigatus* ss, with an overall prevalence of only 1.2% [10, 11]. Similar results were reported in a later single-centre study conducted in Madrid which included 362 *A. fumigatus* complex isolates from 150 patients with proven or probable aspergillosis, with rates of azole-resistance among *A. fumigatus* ss of 1.8% [43]. Nevertheless, a more recent study from the same group which included 828 *A. fumigatus* ss isolates collected from 29 Spanish hospitals, reported a rate of azole resistance of 5.5%, raising concern about the evolving epidemiology in Spain. In this study, the most common underlying mechanism of resistance was mediated by Cyp51A mutations, mainly TR34-L98H substitutions, with striking geographical variations across the country. More specifically, resistant isolates were identified in 8 cities in northern Spain, the Mediterranean coast (including Barcelona) and Madrid [12]. Similarly, in our study, 90% of the isolates in which molecular sequencing was available harbored Cyp51A mutations, predominantly TR34 substitutions with a pan-azole resistant phenotype,

which point towards an environmental origin of resistance. In addition, most patients of our cohort had not been previously exposed to antifungals, further reinforcing this hypothesis. Noteworthy, only 30% of our isolates could be studied for Cyp51A mutations. Given the worrisome increase of ARAF strains in our setting, an urgent need for implementing rapid and reliable diagnostic tools to early identify azole-resistant strains arises, thus facilitating surveillance programs and, ultimately, improving treatment adequateness and outcomes.

An important finding of our study is that most of ARAF isolates were considered as colonizers in non-immunosuppressed individuals with structural lung disease and low associated mortality. Most large

epidemiological studies exclusively describe the prevalence of ARAF among culture-positive *A. fumigatus* isolates without further assessing whether these isolates represent colonization or are associated with fungal disease. In fact, the only few studies that have evaluated the clinical impact of *A. fumigatus* isolation have reported colonization rates of 56% [10, 11], which are lower than those observed in our cohort. This might be explained by differential baseline characteristics of our study population since our hospital is a referral center for patients with chronic lung disease, including cystic fibrosis.

The overall rate of IA among patients with ARAF isolation was 9%, with all cases diagnosed in severely immunocompromised patients who frequently received an inadequate azole-based empirical treatment and associated very high mortality rates. Similar to our results, azole-resistant invasive aspergillosis has been associated with IAET, increased need of antifungal change and higher mortality when compared to IA due to susceptible strains [24, 44]. Clinical documentation of azole-resistant IA cases in Spain remains sparse, probably due to lower resistance rates at a national level compared to other countries and a potential underdiagnosis in centres where antifungal susceptibility testing is not systematically performed. However, Monzo-Gallo et al. warned of an increase in azole-resistant IA in Barcelona with a report of three cases of ARAF-related IA within a one-year period at their institution [21].

Compared to previous literature, our study is among the first to comprehensively assess the clinical significance of ARAF isolates through the integration of microbiological findings with granular patient-level data. This is particularly relevant because some experts propose that, in settings exceeding 10% prevalence of azole-resistant isolates, local protocols should be changed and define an alternate non-azole agent as first line antifungal treatment [28]. Conversely, given the high rate of colonization and low overall mortality, we consider that local epidemiology alone is insufficient to guide universal recommendations for empirical antifungal therapy. Instead, individual patient risk factors are of utmost importance to guide the antifungal empirical strategy. Consequently, in our setting, a non-azole agent should be reserved for first-line therapy in high-risk immunosuppressed patients with suspected IA until ARAF is ruled out, in order to improve treatment adequacy and outcomes. This tailored approach has important clinical implications because the current alternative to azoles in clinical practice is L-Amb, which associates substantial toxicity and is only available in intravenous formulation. New antifungal compounds have shown promising results with improved efficacy and better safety profile. Unfortunately, most of these novel agents remain investigational and are only available through compassionate use or clinical trial enrolment which precludes its early use in routine clinical practice.

The main strength of the present study is the inclusion of a large number of *A. fumigatus* isolates in which an antifungal susceptibility testing was performed systematically throughout the study period which enabled a true estimation of the prevalence of ARAF among culture-positive isolates in our setting. However, some limitations should be acknowledged. First, due to the retrospective design some information may have been lost with residual confounding. Second, this was a single-centre study, limiting the generalizability of our findings to other health-care facilities. Third, only patients with a positive *A. fumigatus* culture were included, potentially underestimating the prevalence of azole-resistant

aspergillosis in patients with positive biomarkers and no microbiological isolation. Finally, we only included patients with an ARAF isolation so a clinical comparison with patients with azole-susceptible *A. fumigatus* was not performed.

CONCLUSION

In conclusion, the prevalence of ARAF in our setting was high, mainly identified as a colonizer in non-immunosuppressed individuals. Invasive disease was infrequent but associated with high rates of inadequate treatment and mortality. In our setting, early empirical antifungal treatment against ARAF should be considered in high-risk immunosuppressed patients with invasive aspergillosis until azole-resistance is excluded.

Declarations

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AUTHORSHIP

Gonzalo Escudero, Adaia Albasanz-Puig, Maria Teresa MartÍn-Gomez and Anna Falcó-Roget contributed to the conceptualization and methodology of the study. Gonzalo Escudero, Adaia Albasanz-Puig, Maria Teresa MartÍn-Gomez and Anna Falcó-Roget contributed to data curation and investigation. Gonzalo Escudero, Adaia Albasanz-Puig and Anna Falcó-Roget performed the formal analysis and wrote the original draft of the manuscript. All authors contributed to the interpretation of the results, critically reviewed the manuscript, and approved the final version.

DECLARATION OF COMPETING INTEREST

Adaia Albasanz-Puig has enacted consultancy and received honoraria for speaking at educational events from Kite/Gilead, Pfizer, MundiPharma, AstraZeneca. Maria Teresa Martín-Gomez has enacted consultancy and received honoraria for speaking at educational events from Pfizer, Gilead, and Vircell. Ibai Los-Arcos has received honoraria for speaking at educational events from Merck, Shionogi, Pfizer, and Takeda, and has received travel support from Gilead, Merck, Menarini, Shionogi, and Mundipharma for scientific purposes. Òscar Len has received honoraria for speaking at educational events for Pfizer, Astellas, Novartis, and Merck and research funding from Pfizer and Merck.

DECLARATION OF AI-ASSISTED TECHNOLOGIES IN THE MANUSCRIPT PREPARATION PROCESS

During the preparation of this work, the authors used ChatGPT for assistance in language editing and improving the readability of this manuscript. After using this tool/service, the author(s) reviewed and edited the content as needed and take(s) full responsibility for the content of the published article.

DATA AVAILABILITY STATEMENT: for original data requests contact adaia.albasanz@vallhebron.cat.

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Figures

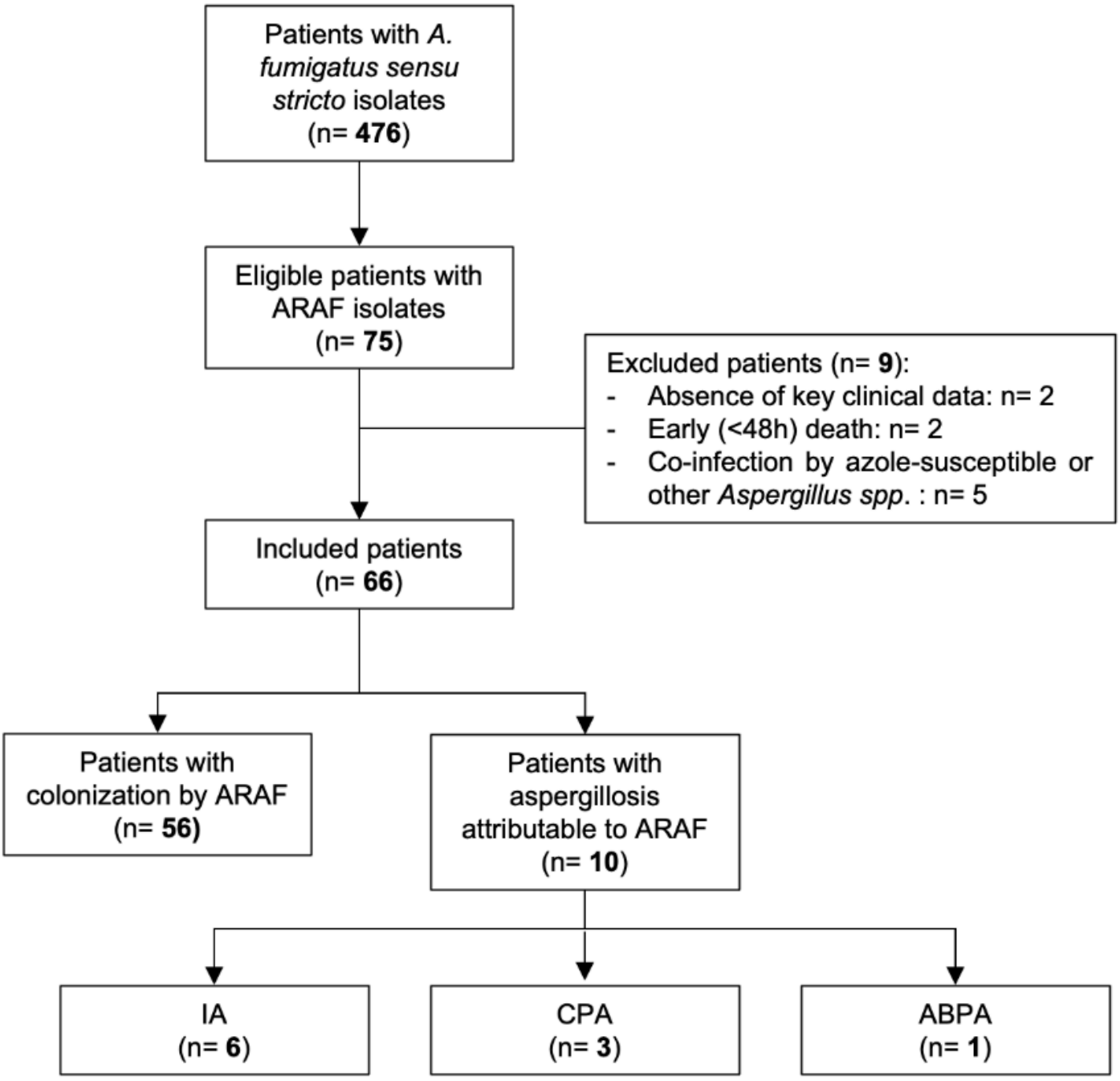


Figure 1

Study cohort and patients' selection.

Abbreviations: ARAF, azole-resistant *Aspergillus fumigatus*; spp., species; IA, invasive aspergillosis; CPA, chronic pulmonary aspergillosis; ABPA, allergic bronchopulmonary aspergillosis.

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