Real-life epidemiology and current outcomes of hospitalized adults with invasive fungal infections

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Lay summary: Current epidemiology of the host and fungi, and IFI treatments are changing. Real-life data on this subject is scarce. We present our most recent evidence to highlight the importance of the ongoing challenges that require further investigation and clinical adjustments.

ABSTRACT

Background: We aimed to describe the current epidemiology of both hosts with invasive fungal infections (IFI) and causative fungi. And detail outcomes of these infections at 12 weeks in a real-life cohort of hospitalized patients.

Methods: Retrospective, observational study to describe IFI diagnosed in a tertiary hospital (February 2017 - December 2021). We included all consecutive patients meeting criteria for proven or probable IFI according to EORTC-MSG and other criteria.

Results: A total of 367 IFI were diagnosed. 11.7% were breakthrough infections, and 56.4% were diagnosed in the intensive care unit (ICU). Corticosteroid use (41.4%) and prior viral infection (31.3%) were the most common risk factors for IFI. Lymphoma and pneumocystis pneumonia were the most common baseline and fungal diseases. Only 12% of IFI occurred in patients with neutropenia. Fungal cultures were the most important diagnostic tests (85.8%). The most frequent IFI were candidemia (42.2%) and invasive aspergillosis (26.7%). Azole-resistant *candida* strains and non-*fumigatus aspergillus* infection represented 36.1% and 44.5% of the cases, respectively. Pneumocystosis (16.9%), cryptococcosis (4.6%) and mucormycosis (2.7%) were also frequent, as well as mixed infections (3.4%). Rare fungi accounted for 9.5% of infections. Overall IFI mortality at 12 weeks was 32.2%; higher rates were observed for Mucorales (55.6%), Fusarium (50%) and mixed infections (60%).

Conclusions: We documented emerging changes in both hosts and real-life IFI epidemiology. Physicians should be aware of these changes to suspect infections and be aggressive in diagnoses and treatments. Currently, outcomes for such clinical scenarios remain extremely poor.

INTRODUCTION

The World Health Organization (WHO) recently published a list of priority fungal pathogens that pose the greatest threat to public health due to either difficult diagnosing or potential resistance to available treatments[1]. Even though invasive fungal infections (IFI) are a rather complex group of severe nature with high morbidity and mortality rates[2,3], real-life information on hospitalized patients with IFI in the current era is scarce. Compounding the problem is the fact that challenges presented by these infections are of major importance.

Over the past years, new hosts susceptible to fungal infections have been reported[4,5]. However, there is no detailed information of who these hosts are; how many patients they represent or where hospitalization takes place. These details are important. These infections may change the classical clinical picture of IFI and affect patients in different hospital areas where attending doctors of varying specialization profiles may have neither a high index of suspicion for such infections nor the expertise to treat them effectively. Moreover, the changing epidemiology of IFI is becoming increasingly complex: the number of resistant and rare fungi, especially in breakthrough IFI, is on the rise[6,7]. There are novel diagnostic tools and antifungals with specific advantages and disadvantages; however, real-life experiences using such drugs and approaches have not been highly reported. Finally, current information on the overall prognosis of these patients beyond randomized studies is poorly reported in literature.

In this paper, we aimed to describe those patients presently diagnosed with fungal infections, the most useful diagnostic techniques and epidemiology of IFI in a real-life tertiary hospital. We also aimed to report the outcomes of these infections at 12 weeks.

MATERIAL AND METHODS

Study design, patients and data collection

We performed a retrospective, observational study to describe all consecutive IFI diagnosed in Hospital Clinic of Barcelona, Spain. The 700-bed university center provides care to a population of 500 000 inhabitants and is a reference institution for a high number of hematologic and solid malignancies, complex and intensive care cases, and allogenic and solid organ transplantations. The study included all adult patients who received an IFI diagnosis between February 2017 and December 2021.

A total of 770 fungal isolations from cultures and real-time polymerase chain reaction (RT-PCR) detection, as well as positive fungal biomarkers were subjected to review by a consensus team (PMG, PPA, MC, CL, FA, MB, AS and CGV). We included only those 367 episodes of patients who met criteria for proven or probable IFI according to either the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group (EORTC-MSG)[6]; AspICU algorithm[7]; influenza-associated pulmonary aspergillosis (IAPA) criteria[8]; coronavirus disease-associated pulmonary aspergillosis (CAPA) criteria[9]; or chronic necrotizing aspergillosis[10]. This team also agreed on whether or not patient mortality was related to the fungal infection.

Data was introduced into a specific database created for this research. We collected data on demographics, underlying diseases, clinical variables, microbiology, treatment and outcomes. The day of IFI diagnosis was when the patient underwent the first diagnostic test. For patients whose diagnosis came from post-mortem examination, the day of death was considered to be the day of diagnosis. Breakthrough fungal infection was defined as those patients who had been receiving antifungal treatment for any reason for at least seven days before IFI onset. Neutropenia was considered as that less than 500 neutrophils for more than five days. Corticosteroid use was defined by either a dose of prednisone of more than 20 mg per day for

two weeks or a single dose of methylprednisone of more than 1 mg per kg per day. Viral co-infection was considered as the occurrence of a respiratory virus infection or viral reactivation in immunosuppressed patients in the month previous to IFI or during the first week of diagnosis.

The overall response was classified as either success or failure to treatment. Success included total and partial responses. Total response comprised the resolution of symptoms and radiological improvements when present, while partial response, some clinical and radiological improvements. Failure included stable disease without clinical changes or mild radiological improvements and disease progression with clinical and/or radiological deterioration.

Laboratory procedures

Microbiological tests included cultures from blood, cerebrospinal fluid, respiratory samples (bronchoalveolar lavage [BAL], bronchoalveolar aspirate [BAS] and sputum) and all types of biopsy samples. Sputum was considered as a representative sample with more than 25 neutrophils/field and less than 10 squamous epithelial cell/field according to Murray-Washington criteria.

We performed follow-up testing with fungal RT-PCR detection and biomarkers, including galactomannan and *Cryptococcus* antigen tests. The threshold used to consider a positive galactomannan antigen was either an optical density index ≥ 0.5 in serum in two determinations or ≥ 0.7 in one BAL fluid sample from a susceptible host. The antifungal susceptibility of the isolates was determined in accordance with the CLSI M27-S3 document[11]. *In vitro* antifungal activity was studied via the application of either a commercial microdilution method (YeastOne Sensititre, TREK Diagnostic Systems, Independence, Ohio) or an Etest (bioMérieux SA, Marcy L'Etoile, France). Episodes due to more than one microorganism but in the same site simultaneously were considered mixed infections.

Statistical analysis

The qualitative variables were described as absolute and relative frequencies, while continuous variables were presented using the median and interquartile range (IQR). The analysis was performed with SPSS version 27.0 software. The survival analysis was done via Kaplan-Meier curves that compared the major types of IFI. The analysis also served to distinguish specific mortality rates related to IFI.

Ethics

This observational study was conducted according to the terms and regulations of the local institutional review boards and approved by the Ethics Committee.

RESULTS

Patient characteristics

There was a total of 150.740 hospitalized admissions during the study period. Of these, 367 (0.25%) proven or probable IFI episodes were documented, representing a total of 24.3 cases per 10 000 admissions. The median age of patients was 62 (21-94) years and most were males (244, 68.3%). Table 1 details the main patient characteristics. A total of 43 (11.7%) episodes were breakthrough fungal infections, mainly to isavuconazole (12, 27.9%), fluconazole (11, 25.6%), posaconazole (9, 20.9%) and voriconazole (4, 9.3%). Particularly, most breakthrough invasive aspergillosis occurred while patients were receiving isavuconazole (25%) or posaconazole (37.5%) prophylaxis. The most common underlying condition associated with breakthrough fungal infections was hematologic malignancies (24, 55.8%), follow by stem cell transplantations (17, 39.5%) and solid organ transplantations (9, 20.9%).

Current diagnosis and epidemiology of IFI

One or more of the following methods was used to identify IFI. Fungal cultures diagnosed 315 (85.8%) episodes: 1) blood culture (157, 49.8%: 155 *Candida*, 1 *Saccharomyces* and 1 *Fusarium*); 2) BAL fluid culture (118, 37.5%; 56 *Aspergillus spp.*, 50 *Pneumocystis spp.*, 3 *Cryptococcus spp.* and 1 for *Rhizopus*, *Coccidioides*, *Scedosporidium*, *Paecilomyces* and *Fusarium*); 3) biopsy-obtained tissue culture (22, 6.3%: 8 *Aspergillus*, 3 *Alternaria*, 3 *Fusarium,* 2 *Rhizopus*, and 1 of each of the following cases *Exophiala*, *Arthrocladium*, *Epidermophyton*, *Absidia, Syncephalastrum* and *Candida*); 4) good-quality sputum culture (10, 3.2%: all *Aspergillus*); 5) cerebrospinal fluid culture (7, 2.2%: 6 *Cryptococcus* and 1 *Histoplasma*); 6) other (2, 0.6%: 1 *Cryptococcus* and 1 *mucor*). Galactomannan antigen testing was the only microbiological test in 24 probable aspergillosis (24.5%). Fungal RT-PCR diagnosed 17 (4.6%) episodes: 9 *Pneumocystis*, 4 *Histoplasma*, 2 *Fusarium* and 1 of each of the following *Aspergillus* and *Lictheimia*.

Invasive fungal infections were classified as proven and probable in 205 (55.9%) and 162 (44.1%) cases, respectively. Table 2 details the epidemiology of currently diagnosed IFI. The most common IFI were candidemia (42.2%), invasive aspergillosis (26.7%), and pneumocystosis (16.9%). Azole-resistant *candida* strains and non-*fumigatus aspergillus* infection represented 36.1% and 44.5% of cases, respectively. Table 1 describes the most important characteristics of patients with these IFI. A total of 35 (9.5%) cases were infrequent fungi. Mixed infections accounted for 3.4% of episodes. Figure S2 details IFI epidemiology and ICU admission by year.

Treatment and outcomes

Antifungal treatment was administered in 354 episodes, with anidulafungin, isavuconazole, fluconazole and B amphotericin being the most common drugs used.

The most frequent antifungal for Candidemia was anidulafungin (65, 41.9%), followed by fluconazole (47, 30.3%) and micafungin (8, 5.2%). Patients with aspergillosis received isavuconazole (55, 59.1%); 36 were monotherapeutic and 19, a combination of amphotericin-B and isavuconazole. Voriconazole (28, 30.1%) was the second most used antifungal for aspergillosis. Patients with pneumocystis pneumonia most received sulfamethoxazole and trimethoprim (53, 85.5%). Only 4 (6.5%) were on clindamycin and primaquine; 5 (8.1%) had combined therapy with caspofungin. Supplementary material details all other treatments.

Figure S1 and table S1 in supplemental material describes overall response to treatment at weeks 4 and 12. Figure S2 shows IFI trends by year and its relation with ICU admission. Figure S3 presents a trend analysis of azole-resistant invasive candidiasis over time. Table S2 shows mortality rates at 12 weeks since diagnosis attributable to IFI. Overall, 12-week mortality was 38.7% (n = 142) and 118 (83%) were attributable to IFI. Figure 1 lists survival per syndrome.

DISCUSSION

The incidence of IFI diagnosed during the study period was 24.3 cases per 10 000 admissions, with most cases being candidemia, invasive aspergillosis and pneumocystosis. Breakthrough infections accounted for 11.7% of IFI, a relative new entity with unclear management even nowadays. Remarkably, 12-week mortality was extremely high. We have observed important changes in the epidemiology of the host and type of fungi, as well as diagnostic tools and treatment compared with previous reports in literature.

Significant epidemiological changes have been detected in patients with IFI compared to those classically at higher risk[12–14]. For instance, individuals with hematologic malignancies accounted for only 23% of patients in the cohort and only 12% had neutropenia. This figure dropped to 7% in the candidemia subgroup. It is also important to note that the most common hematologic comorbidity currently associated with IFI in our cohort was lymphoma. Patients with this condition mainly had pneumocystis pneumonia, candidemia or cryptococcosis. Holding a high index of suspicion for IFI in these patients may be key for early diagnosis and treatment and an improved prognosis. Patients with viral co-infection, primarily coronavirus or influenza virus, and especially those in the ICU, have emerged as an important high-risk group.

The rising incidence and devastating outcomes of severe influenza and COVID-19-associated fungal infections[15–19] have been previously reported. Viruses disintegrate the mucoses, paralyse the immune system and intrinsically secrete Il-10. All of these factors result in the replacement of Th1 response by Th2, thereby facilitating the pathogenesis of IFI[20]. Corticosteroids and chronic lung disease continued to be important factors in facilitating mold infections. Patients with solid cancer have also emerged as another high-risk group. It is noteworthy that candidemia, aspergillosis and pneumocystosis have been frequently documented in this population. In our study, we observed that 20% of IFI occurred in patients with chronic kidney disease. Treatment for these patients is challenging. Further studies are

needed to assess the most appropriate treatment regimens and the impact of adapting antifungal doses, so as to prevent toxicity and poorer patient outcomes.

Invasive candidiasis remained the most common IFI, except for patients with hematologic malignancies in whom aspergillosis was more frequent. Remarkably, non-albicans candida was the most prevailing species, with *Nakaseomyces glabrata (Candida glabrata)* being the most frequent. Echinocandins were the most used treatment. Current ecology and the high efficacy documented in several studies[21–23] support the drug's role as a main initial antifungal treatment for candidemia. Early stepdown to fluconazole in infections caused by susceptible strains with a controlled source of infection is advisable[23]. In our study, 12-week mortality was high (31%), albeit lower than that in other classical series[24–26].

Aspergillosis was the second most frequent IFI in our patients. It was interesting that cultures comprising the most frequent testing method for diagnosis. Only 24.5% of cases were diagnosed with galactomannan antigen in serum or BAL. This fact reflects the low positive predictive value for both non-neutropenic patients and high-risk individuals with hematologic malignancies who received antifungal prophylaxis[27–29]. It is also important to highlight the changing epidemiology reported in our series, in which 44.4% of aspergillus infection was non-fumigatus.

COVID-19-and-influenza-associated pulmonary aspergillosis has been commonly documented. These patients represented the most common group of individuals with aspergillosis infections. Moreover, 20% of ICU-admitted patients with a severe influenza infection or COVID-19 were previously reported to have invasive aspergillosis[18,19]. This clinical scenario is associated with high mortality. Furthermore, 15% of patients with invasive aspergillosis most of which were subacute/chronic forms had solid malignancies. The risk of subacute invasive pulmonary aspergillosis in this population has been well described, especially in patients with primary or metastatic lung cancer[30]. In fact, most patients with invasive aspergillosis (62%) had predisposing factors such as a viral coinfection, corticosteroid therapy and chronic lung disease,

which are also frequent in solid malignancies. These epidemiological changes are of the utmost importance. Studies determining the sensitivity and specificity of most diagnostic techniques for aspergillosis and trials evaluating the effectiveness of antifungal drugs are often performed in a hematologic population, especially in patients with neutropenia[31,32]. Future studies should describe in detail the clinical forms of aspergillosis in these populations, provide guidance on the use of the most robust diagnostic techniques and determine the optimal treatment strategy. It would be of special interest to determine the most suitable treatment for breakthrough aspergillosis as it relates to azoles, given that the type of infection accounts for 16% of diagnosed cases of invasive aspergillosis. Information about the best treatment options is still lacking. Current 12-week mortality in this real-life cohort of patients with aspergillosis was high (44.9%) compared with those described in trials[31,32], reflecting the challenge posed by this new epidemiology.

Pneumocystis pneumonia has been often diagnosed in patients receiving chemotherapy and immunosuppressors. It has also appeared frequently as a suprainfection after respiratory viral diseases. Classically, this infection has been related with people living with HIV (PLWH), whereas in this study PLWH accounted for only 8% of individuals with pneumocystis infection. In contrast, patients with hematologic malignancies, especially those with lymphoma and multiple myeloma, solid organ transplantation and solid malignancies comprised the new clinical scenario of this infection. This observation is important, because clinicians will need to be aware of the possibility of such infections to provide an early diagnosis and treatment.

Additionally, we observed rare types of fungi in 9% of IFI, most of which were diagnosed by a culture or RT-PCR performed on a biopsy sample. This is relevant, as it reflects the fact that diagnosis of certain types of invasive fungal infections can only be made using aggressive techniques like biopsies. Treatment of these types of infections remains a challenge. Also, the mortality rate remains high, especially for those with Mucorales, Fusarium and mixed infections.

Our study has several limitations. It was a retrospective and descriptive study from a particular geographic area without specific endemic mycosis. It is possible that in other geographical areas, IFI frequency may be different, including perhaps the hosts identified. Second, the low number of some cases of mycoses precludes further host description or treatment analyses. We could not specify our autopsy rate per IFI diagnoses, as data were collected as a biopsy sample. Finally, this study was non-interventional; therefore, some diagnostic methods may have been underused by the attending physicians.

As a conclusion, emerging changes are occurring in current epidemiology of the host and type of fungi, as well as diagnostic tools and treatments per IFI. Non-*albicans candida*, non-*fumigatus aspergillus*, and rare types of moulds and yeasts have become more frequent. Physicians should be aware of these changes in order to suspect infections, so as to be aggressive subsequently in diagnosis and administer early treatments. Given difficulties in diagnosing and treating these patients, we recommend creating multidisciplinary fungal infection teams to perform cross-disciplinary work throughout the hospital.

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Conflict of Interest: PP-A has received honoraria for talks on behalf of Merck Sharp and Dohme, Lilly, ViiV Healthcare and Gilead Science. PP-A has participated in advisory boards for Gilead

Science. CG-V has received honoraria for talks on behalf of Gilead Science, Merck Sharp and Dohme, Pfizer, Jannsen, Novartis, Lilly and a grant support from Gilead Science and Merck Sharp and Dohme. AS has received honoraria for talks on behalf of Merck Sharp and Dohme, Pfizer, Novartis, Angelini, as well as grant support from Pfizer. OP has received honoraria for talks on behalf of MSD and Qiagen, and expertise for Sanofi.

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TABLES

Table 1. Characteristics of patients diagnosed with invasive fungal infection.

Patient Characteristic	All cases (N = 357)	Candidemia (n = 155)	Aspergillosis (n = 98)	Pneumocystis (n = 62)
Demographics				
Median age, years (IQR)	62 (21-94)	64 (24-91)	65 (21-94)	55 (25-83)
Male sex	244 (66.5%)	104 (67.1%)	64 (65.3%)	41 (66.1%)
Main comorbidities				
Hematologic malignancy*	86 (23.4%)	20 (12.9%)	36 (36.7%)	13 (21%)
HSCT	29 (7.9%)	4 (2.6%)	13 (13.3%)	2 (3.2%)
Solid organ transplantation	60 (16.3%)	22 (14.2%)	18 (18.4%)	10 (16.1%)
Solid organ malignancy**	67 (18.3%)	35 (22.6%)	15 (15.3%)	10 (16.1%)
HIV infection	50 (13.6%)	6 (3.9%)	3 (3.1%)	5 (8.1%)
Chronic lung disease	88 (24%)	34 (21.9%)	34 (34.7%)	8 (12.9%)
Chronic kidney disease	74 (20.2%)	32 (20.6%)	20 (20.4%)	10 (16.1%)
Diabetes mellitus	73 (19.9%)	40 (25.8%)	20 (20.4%)	5 (8.1%)
Heart disease	74 (20.33%)	44 (28.4%)	19 (19.4%)	6 (9.7%)
Liver disease	67 (18.4%)	35 (22.6%)	13 (13.3%)	10 (16.1%)
Other predisposing factors				
Corticosteroid therapy	152 (41.4%)	51 (32.9%)	61 (62.2%)	20 (32.3%)
Neutropenia	47 (12.8%)	12 (7.7%)	24 (24.5%)	2 (3.2%)
Viral coinfection***	115 (31.3%)	34 (21.9%)	46 (46.9%)	20 (32.3%)
Immunosuppressors therapy	107 (29.3%)	29 (18.7%)	44 (44.9%)	17 (27.4%)
Chemotherapy	90 (24.5%)	23 (14.8%)	33 (33.7%)	21 (33.9%)
GVHD	16 (4.4%)	1 (0.6%)	13 (13.3%)	1 (1.6%)
ICU	207 (56.4%)	99 (63.9%)	53 (54.1%)	31 (50%)
Breakthrough infection	43 (11.7)	14 (9%)	16 (16.3%)	-

* Lymphoma was the most common type (27, 32.1%), followed by acute myeloid leukemia (22, 26.2%), multiple myeloma (11, 13.1%), lymphoid acute leukemia (7, 8.3%), lymphoid chronic leukemia (7, 8.3%) and myelodysplastic syndrome (5, 6%).

** Lung cancer was the most frequent type (12, 17.9%), followed by breast cancer (9, 13.4%); colorectal, prostate and urinary tract cancer (8, 11.9%); liver cancer (5, 7.5%); and pancreas and ENT cancer (4, 6%), respectively.

*** 39.1% (n = 18) of invasive aspergillosis were associated to SARSCoV2 and 6.5% (n = 3) influenza.

GVHD, graft-versus-host disease

Table 2. Current invasive fungal infection epidemiology

IFI epidemiology	All cases/microorganism (N = 367)/(N = 380)
Candidemia*	155 (42.2%) / 158 (41.6%)
Nakaseomyces glabrata	47 (30.3%) / 48 (30.4%)
Candida albicans	44 (28.4%) / 46 (29.1%)
Candida parapsilosis	35 (22.6%) / 36 (22.8%)
Candida tropicalis	11 (7.1%) / 12 (7.6%)
Candida krusei	7 (4.5%) / 8 (5.1%)
Other	8 (5.1%) / 8 (5.1%)
Aspergillosis**	98 (26.7%) / 107 (28.1%)
Isolated	72 (73.5%) / 81 (75.7%)
Aspergillus fumigatus	43 (59.7%) / 45 (55.5%)
Aspergillus flavus	9 (12.5%) / 11 (13.6%)
Aspergillus terreus	8 (11.1%) / 9 (11.1%)
Aspergillus niger	5 (6.9%) / 7 (8.6%)
Others	4 (5.5%) / 6 (7.4%)
Unknown spp.	3 (4.2%) / 3 (3.7%)
Unknown	26 (24.3%)
Pneumocystosis***	64 (17.4%) / 64 (16.8%)
Cryptococcosis	17 (4.6%) / 17 (4.5%)
Mucormycosis***	10 (2.7%) / 10 (2.6%)
Fusariosis***	7 (1.9%) / 7 (1.8%)
Histoplasmosis	5 (1.4%) / 5 (1.3%)
Alternariosis	4 (1.1%) / 5 (1.3%)
Epidermophyton infection	1 (0.3%) / 1 (0.3%)
Paecilomycosis	1 (0.3%) / 1 (0.3%)
Saccharomycosis	1 (0.3%) / 1 (0.3%)

Scedosporidiosis	1 (0.3%) / 1 (0.3%)
Coccidioidomycosis	1 (0.3%) / 1 (0.3%)
Arthrocladium infection	1 (0.3%) / 1 (0.3%)
Exophiala infection	1 (0.3%) / 1 (0.3%)

* Mixed candidemia 3/155 (1.9%) episodes; 1) One patient with ENT cancer had septic shock due to candidemia by *Candida parapsilosis* and *C. krusei;* 2) a patient with a renal transplant had polymicrobial endocarditis by *Enterococcus faecium*, *Candida albicans* and *Nakaseomyces glabrata;* and 3) A patient with cirrhosis and diabetes had septic shock due to C*andida albican*s and *Candida tropicalis.*

** Mixed aspergillosis 4/98 (5.6%) episodes: 1) One patient with liver cirrhosis and abdominal septic shock had pulmonary aspergillosis due to *Aspergillus fumigatus* and *Aspergillus niger*; 2) A patient with multiple myeloma admitted for abdominal septic shock had pulmonary aspergillosis due to *Aspergillus fumigatus* and *Aspergillus terreus;* 3) A patient with chronic necrotizing aspergillosis was admitted with an acute episode due to *Aspergillus fumigatus* and *Aspergillus flavus;* and 4) A patient with COVID-19-associated pulmonary aspergillosis due to *Aspergillus terreus* and *Aspergillus niger*.

*** Mixed infections 5/367 (1.4%) episodes: 1) A patient had lung cancer and a pulmonary mycetoma with isolation of *Aspergillus flavus* and *Alternaria alternata*; 2-3) Two patients with a cardiac transplant and severe viral infection by influenza A requiring ICU, respectively, had *Pneumocystis* spp. pneumonia and invasive pulmonary aspergillosis concomitantly. 4) Another patient with multiple myeloma had invasive pulmonary aspergillosis due to *Aspergillus fumigatus* and mucormycosis due to *Absidia* spp.; and 5) a patient with COVID-19-associated pulmonary aspergillosis also had a disseminated infection due to *Fusarium oxysporum.*

FIGURES

Figure 1.

Kaplan-Meier survival curve comparing different main IFIs.

IFI, invasive fungal infection