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Comparison of Patients With or Without COVID-19 and Without Hematological Diseases Treated for Invasive Pulmonary Aspergillosis: A 5-Year Retrospective Cohort Study with Propensity-Based Adjustment

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Background. Our aim was to compare epidemiological, clinical and treatment characteristics, and outcomes between patients with diagnoses of coronavirus disease 2019–associated pulmonary aspergillosis (CAPA) or putative invasive pulmonary aspergillosis (PIPA), without hematological cancers.

Methods. Retrospective, monocentric comparative observational cohort study, including nonhematological patients treated for invasive pulmonary aspergillosis between 2018 and 2022. Primary study end points were risk factors for 30-day mortality and clinical failure. To account for the imbalance in antifungal treatment allocation, a propensity score weighting approach was adopted.

Results. A total of 209 patients were included, 93 (44.5%) with CAPA and 116 (55.5%) with PIPA; 144 (68.9%) we admitted to the intensive care unit. Patients with PIPA had higher Charlson Comorbidity Index values (mean [SD], 5.8 [2.6]; range, 0–14) and higher prevalences of chronic obstructive pulmonary disease (30.7%), solid cancer (36.8%), liver cirrhosis (12.3%), and concomitant immunosuppressive therapies (26.1%). Patients with CAPA received more invasive mechanical ventilation (70.5%) and corticosteroids (90.1%), more frequently had positive galactomannan (GM) results with bronchoalveolar lavage (80.5%), and had longer mean hospital stays (62.7 [SD, 52.1; range, 8–276] days) and intensive care unit stays (36 [30.7; 2–168] days). No differences in clinical cure or mortality rates were observed between groups. In multivariable analysis, isavuconazole was the only independent factor for clinical cure, reported also in the propensity score matching analysis (odds ratio, 0.41 [95% confidence interval, .16–1.03]; $P = .06$). A positive serum GM result was independently associated with 30-day mortality (hazard ratio, 1.78 [95% confidence interval, 1.02–3.10]; $P = .04$).

Conclusions. Patients with CAPA have fewer comorbid conditions and higher fungal burden than those with PIPA, but clinical outcomes are similar between groups. Isavuconazole was an independent predictor for clinical cure, and serum GM positivity an independent predictor for 30-day mortality.

Keywords. aspergillosis; CAPA; COVID-19; critical care; immunocompromised.

The European Organization for Research and Treatment of Cancer/Mycosis Study Group (EORTC/MSG) definitions for invasive pulmonary aspergillosis (IPA) specify the presence of commonly accepted host factors predisposing to aspergillosis: neutropenia, hematological cancers, bone marrow or solid organ transplantation, and graft-vs-host disease [1]. Since the development of the original guidelines, additional host factors, such as severe inherited immunodeficiencies and

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low CD4 cell count, have been included in the revised guidelines in 2020 [2]. New populations at risk for IPA have also been recognized among the scientific community, including immunocompetent patients [3]. A definition of putative IPA (PIPA) was developed by Blot et al [4] in 2012 and then modified by Schauwvlieghe et al [5] in 2018 to classify patients at risk of IPA in intensive care units (ICUs). However, this definition has also been applied in studies assessing patients treated in nonintensive settings [6].

A strong association between IPA and severe acute respiratory syndrome (SARS-CoV-2) severe pneumonia has been demonstrated, with an incidence rate of 0.7%–7.7% [7], defined as coronavirus disease 2019 (COVID-19)–associated pulmonary aspergillosis (CAPA) [8]. Compared with IPA in immunocompromised patients, CAPA is clinically more challenging to manage due to an unusual clinical and radiological presentation and more frequent observation in older patients [9, 10]. In the postpandemic scenario, a more detailed microbiological, clinical, and therapeutic characterization among all hospitalized patients at risk for IPA, not only those critically ill, is essential. This characterization can assist in the development of new definitions for medical wards and elderly populations. Studies directly comparing PIPA and CAPA in nonhematological patients admitted to ICU and medical and surgical wards are required.

During the COVID-19 pandemic, the newly introduced antifungal agent isavuconazole was quickly adopted for patients with IPA. However, the tolerability and efficacy profile of isavuconazole compared with voriconazole is undefined, despite the post hoc analysis from the VITAL and SECURE trials [11]. Data are particularly missing for elderly patients.

The aim of the current study was to compare demographic, clinical, microbiological, radiological, and treatment characteristics, 30- and 90-day mortality rates, clinical cure, and IPA infection relapse between patients with CAPA and those with PIPA. Risk factors for 30-day mortality and clinical failure were also assessed. Finally, a subanalysis of comparative outcomes was performed in selected patients with IPA treated with isavuconazole or voriconazole as the primary regimen, without any switch to a second-line treatment.

METHODS

Study Design and Clinical Definitions

We conducted a retrospective, observational monocentric cohort study to include consecutive adult patients with an infectious diseases consultation and treatment for IPA in ICUs and medical and surgical wards at the University Hospital of Modena, between January 2018 and December 2022. Patients with an IPA diagnosis were screened. Cases were retrospectively reclassified according to the currently available definitions. Patients with concomitant or recent COVID-19 (within ≤1 month) and with diagnoses according to the definition of "probable," "possible," or "proven" IPA by Koehler et al [8] were grouped as having CAPA. Patients without a diagnosis of recent SARS-CoV-2 infection (within ≤1 month) and identified with "putative" or "proven" IPA (according to the modified-AspICU algorithm of Schauwvlieghe et al [5] and/or "probable," "possible," or "proven" IPA according to the EORTC/MSG definition [2] were classified as having PIPA. SARS-CoV-2 infection was defined as a positive reverse-transcription (RT) polymerase chain reaction (PCR) or antigenic test result with a respiratory specimen.

Criteria specified the exclusion of patients (1) affected by other forms of aspergillosis (non-IPA), (2) with any type of hematological neoplasia, (3) who received antifungal agents as prophylaxis, or (4) who received antifungal agents for other concomitant fungal infections. The study was approved by the ethics committee Comitato Etico Indipendente Area Vasta Emilia Nord (no. 624/2023/OSS/AOUMO).

Data Collection

For each patient, demographic and clinical data at time of diagnosis were collected, particularly age, sex, year and ward of diagnosis (medical, surgical, or ICU), invasive mechanical ventilation (IMV), comorbid conditions and Charlson Comorbidity Index (CCI), and use of steroids or other immunosuppressive therapies. Symptoms related to aspergillosis and Sequential Organ Failure Assessment (SOFA) score were also obtained. Radiological patterns were derived from written reports and by reviewing images when necessary. For antifungal treatment, we collected data about the molecule used (voriconazole, isavuconazole, and liposomal amphotericin B, L-Amb), as the first regimen or as a possible second-line treatment, reason for switch, treatment duration, and associated adverse events (AEs).

Microbiological Analyses

For aspergillosis identification, all respiratory samples were evaluated at microscopic examination, to detect the presence of fungal hyphae or spores. Culture examinations were always performed, and, when results were positive, *Aspergillus* species was identified through matrix-assisted laser desorption/ionization–time of flight (MALDI-TOF) when feasible and/or with the help of macroscopic and microscopic examination of the colonies. Susceptibility to voriconazole, isavuconazole, and L-Amb was determined using standardized broth microdilution methods (Sensititre Yeast One ITAMYUCC test; Thermo Scientific). Minimum inhibitory concentrations were interpreted according to guidelines of the Clinical and Laboratory Standards Institute, using the break point established only for voriconazole for *Aspergillus fumigatus* and the epidemiological cutoff for other *Aspergillus* species [12, 13].

Galactomannan (GM) was detected with an enzyme-linked immunosorbent assay (Platelia *Aspergillus* assay; BioRad),

and for diagnostic purposes we considered a positivity cutoff of 0.5 optical density index for serum and of 1.0 optical density index for respiratory samples. For 1,3-β-D-glucan (BDG) in serum, we used the Fungitell assay (Associates of Cape Cod), with a positivity cutoff of 80 pg/mL.

DNA extraction for PCR and RT-PCR analyses was performed on an ELITe InGenius automated platform using the *Aspergillus* spp ELITe MGB kit (Elitgroup). DNA was extracted from a 1-mL volume of bronchoalveolar lavage (BAL) or bronchoaspirate (BAS) fluid and was eluted in a 200-µL saline solution before DNA amplification with the same platform. The ELITe MGB kit for RT-PCR was CE–in vitro diagnostic validated on a diverse range of sample types. The target region was the ribosomal DNA 18S, and the human β-globin gene was used as an internal standard. The fungal DNA copy number was expressed as copies per milliliter in relation to a ribosomal DNA18S standard curve.

Outcomes

Primary outcomes were defined as follows: 30-day mortality was calculated from the start of therapy, and clinical cure was considered as a substantial improvement in symptoms and/or radiological patterns at the end of treatment. Secondary outcomes were: 90-day mortality (from the start of therapy), infection relapse (defined as recurrence of IPA ≤90 days from the end of treatment in patients who previously experienced clinical cure), length of hospital stay (LOS), and length of ICU stay. The subgroup analysis included selected patients with IPA treated with isavuconazole or voriconazole (as primary regimen without any switch to a second-line treatment) with outcomes of 30- and 90- day mortality, clinical cure, IPA infection relapse, and AEs.

Statistical Analysis

A descriptive analysis of all collected variables was conducted; categorical variables were presented as numbers and percentages, and continuous variables as means with SDs if normally distributed or medians with interquartile ranges if not normally distributed. Univariate analysis assessed differences between groups and risk factors. Fisher exact or χ^2 tests were used for categorical variables, and *t* or Mann-Whitney *U* tests for continuous variables. Statistical significance was defined as a *P* value <.05.

Multivariate analysis was performed using logistic and Cox regression models; significant and clinically relevant variables were included. Results were presented as odds ratios (ORs) or hazard ratios (HRs) with 95% confidence intervals (CIs). Propensity score (PS) matching (PSM) accounted for potential confounding in antifungal treatment allocation. The PSs were calculated using a logistic regression model including relevant covariates. They were then used to perform 1:1 matching between patients treated with voriconazole and those treated with isavuconazole, using the nearest-neighbor method (caliper, 0.2 SD from the logit of the PS). Balance between PSM groups was assessed using standardized mean differences; <0.1 indicated adequate balance, minimizing potential confounding effects.

Kaplan-Meier survival curves were generated to compare 30-day survival from the start of therapy between groups and subgroups and to compare clinical failure among subgroups. Survival distribution comparisons were performed using the log-rank test. Statistical analysis was performed using Stata statistical software, version 17 (StataCorp 2021).

RESULTS

Between January 2018 and December 2022, a total of 209 patients were included, 93 with CAPA (44.5%) and 116 with PIPA (55.5%). Most IPA cases (70%) were diagnosed in ICUs, and 30% were diagnosed in medical wards. In the whole population, the clinical cure rate was 46.6%, and the 30- and 90-day mortality rates were 37.8% and 50.2%, respectively. Finally, 2.5% of patients experienced infection relapse.

Comparison Between CAPA and PIPA Groups

The main demographic, clinical, microbiological, and radiological characteristics, 30- and 90- day mortality rates, and rates of clinical cure and IPA infection relapse in patients with CAPA or PIPA are provided in Table 1. Most cases of IPA (170 of 209 cases [81.3%]) were diagnosed after 2020 (93 as CAPA and 77 as PIPA). The incidence of CAPA increased from 0.19/1000 patient-days in 2020 to 0.25/1000 patient-days in 2021 and decreased to 0.08/1000 patient-days in 2022. The incidence of PIPA increased after 2020, reaching an incidence of 0.19/1000 patient-days in 2022 (Supplementary Figure 1). All CAPA cases were classified as probable. PIPA classifications differed according to the definitions applied: the modified-AspICU algorithm was quite sensitive since 67.2% of cases were classified as putative and only 23.3% did not meet the diagnostic criteria; 70.7% of cases were "nonclassifiable" by the EORTC/MSG definition with only 17.2% classified as probable and 9.5% as possible. Three patients had proven IPA according to both models (Supplementary Table 1).

Compared with patients with PIPA, more of those with CAPA had cases diagnosed in the ICU (89.3% vs 52.6%, respectively; $P < .001$) and, consequently, more underwent IMV (70.5% vs 35.3%; $P < .001$). More patients with CAPA received steroids and tocilizumab during their hospital stay (steroids, 90.1% vs 52.6% for those with PIPA; tocilizumab, 62.3% vs 0.8%; both $P < .001$). Conversely, more patients with PIPA had cases diagnosed in medical wards (46.6% vs 10.8%, respectively; $P < .001$), patients with PIPA had higher CCIs (mean [SD], 3.9 [2.3; range, 0–10] vs 5.8 [2.6; 0–14]; $P < .001$), and more patients with PIPA had chronic obstructive

Table 1. Demographic and Baseline Characteristics, Treatment, and Outcomes in Patients With Coronavirus Disease 2019–Associated Pulmonary Aspergillosis or Putative Invasive Pulmonary Aspergillosis

Characteristic, Treatment, or Outcome	Patients, No. (%)[a]			*P* Value
	Total (n = 209)	CAPA, (n = 93 [44.5%])	PIPA, (n = 116 [55.5%])	
Age, mean (SD; range), y	67.3 (12.3; 23–94)	67.4 (10.4; 34–91)	67.2 (13.6; 23–94)	.91
Male sex	137 (65.5)	70 (75.3)	67 (57.8)	.008
Ward of diagnosis				
ICU	144 (68.9)	83 (89.3)	61 (52.6)	<.001
Medical	64 (30.6)	10 (10.8)	54 (46.6)	<.001
Surgical	1 (0.5)	0 (0)	1 (0.8)	.37
Year of diagnosis				
2018	15 (7.2)	0 (0)	15 (12.9)	.001
2019	20 (9.6)	0 (0)	20 (17.2)	<.001
2020	46 (22.0)	32 (34.4)	14 (12.1)	<.001
2021	81 (38.8)	46 (49.5)	35 (30.2)	.004
2022	47 (22.5)	15 (16.1)	32 (27.6)	.049
Time from admission to IPA, mean (SD; range), d	20.7 (18.9; 1–129)	21.7 (18.2; 2–95)	19.8 (19.6; 1–129)	.47
Comorbid conditions				
CCI, mean (SD; range)	5 (2.62; 0–14)	3.9 (2.3; 0–10)	5.8 (2.6; 0–14)	<.001
Heart disease	58/203 (28.6)	26 (29.2)	32 (28.1)	.86
Hypertension	127/203 (62.6)	58 (65.9)	69 (60)	.39
Vasculopathy	43/203 (21.2)	17 (19.1)	26 (22.8)	.52
Neurological disease	25/203 (12.3)	8 (8.9)	17 (14.9)	.20
Diabetes mellitus	54/203 (26.6)	27 (30.3)	27 (23.7)	.29
Dyslipidemia	57/203 (28.1)	28 (31.5)	29 (25.4)	.34
Renal failure	27/203 (13.3)	12 (13.3)	15 (13.3)	.99
COPD	47/203 (23.2)	12 (13.5)	35 (30.7)	.004
Other pneumopathy	32/203 (15.7)	10 (11.1)	22 (19.3)	.11
Previous tuberculosis	6/203 (3)	1 (1.1)	5 (4.4)	.17
Solid cancer	55/203 (27.1)	13 (14.6)	42 (36.8)	<.001
HIV	2/203 (1)	0 (0)	2 (1.8)	.21
Solid organ transplant	18/203 (8.9)	4 (4.5)	14 (12.3)	.053
Liver cirrhosis	15/203 (7.4)	1 (1.1)	14 (12.3)	.002
Other liver disease	19/203 (9.4)	6 (6.7)	13 (11.4)	.26
Autoimmune disease	22/203 (10.8)	8 (8.9)	14 (12.3)	.45
Active smoker status	33/200 (16.5)	12 (13.5)	21 (18.9)	.45
Concomitant influenza	3/209 (1.44)	1 (1.1)	2 (1.7)	.70
Extrinsic factors				
IMV	103/204 (50.5)	62 (70.5)	41 (35.3)	<.001
Steroids	143/207 (69.1)	82 (90.1)	61 (52.6)	<.001
Steroid duration >3 wk	59/207 (28.5)	25 (29.4)	35 (31.5)	.75
Tocilizumab	54/203 (26.6)	53 (62.3)	1 (0.8)	<.001
Other immunosuppressive therapies	39/204 (19.1)	9 (10.1)	30 (26.1)	.004
Active chemotherapy	18/203 (8.9)	6 (6.8)	12 (10.4)	.37
Concomitant antibiotic therapy	173/199 (86.9)	78 (90.7)	95 (84.1)	.17
Coinfection on respiratory sample				
CMV	48/198 (24.2)	22 (25.6)	26 (23.2)	.70
Pneumocystis jirovecii	27/198 (13.6)	1 (1.2)	26 (23.0)	<.001
Pseudomonas aeruginosa	39/200 (19.5)	21 (24.4)	18 (15.8)	.13
Clinical presentation				
SOFA, mean (SD; range)	4.9 (3.5; 0–17)	4.9 (3.1; 1–17)	4.9 (3.9; 0–17)	.89
Septic shock	33/196 (16.8)	14 (16.9)	19 (16.8)	.99
Hemoptysis	7 (3.4)	1 (1.1)	6 (5.2)	.10
Worsening respiratory insufficiency	168 (80.4)	80 (86.0)	88 (75.9)	.07
Dyspnea	144 (68.9)	62 (66.7)	82 (70.7)	.53
Persistent fever	19 (9.1)	6 (6.5)	13 (11.2)	.24
Recurrent fever	18 (8.6)	3 (3.2)	15 (12.9)	.01

Table 1. Continued

Characteristic, Treatment, or Outcome	Patients, No. (%)[a]			*P* Value
	Total (n = 209)	CAPA, (n = 93 [44.5%])	PIPA, (n = 116 [55.5%])	
Chest pain	3 (1.4)	2 (2.2)	1 (0.9)	.44
Pleural friction rub	1 (0.5)	1 (1.1)	0 (0)	.26
Tracheobronchial pseudomembranes/ ulcerations	3 (1.4)	2 (2.2)	1 (0.9)	.44
CT scan	193/209 (92.3)	81/93 (87.1)	112/116 (96.6)	…
CT findings				
Cavitation	28 (14.5)	11 (13.6)	17 (15.2)	.76
Ground glass	119 (61.7)	65 (80.3)	54 (48.2)	<.001
Consolidation	161 (83.4)	74 (91.4)	87 (77.7)	.01
Nodules	62 (32.1)	21 (25.9)	41 (36.6)	.12
Tree in bud	25 (12.9)	2 (2.5)	23 (20.5)	<.001
Halo sign	6 (3.1)	3 (3.7)	3 (2.7)	.69
Air crescent sign	0 (0)	0 (0)	0 (0)	…
Microbiology				
Culture positive with respiratory sample (≥1)	99/209 (47.4)	43 (46.2)	56 (48.3)	.77
Microscopy on BAL	15/185 (8.1)	5 (6.2)	10 (9.6)	.40
BAL GM positivity (≥1.0)	126/173 (72.8)	62 (80.5)	64 (66.7)	.04
BAL GM, mean (SD; range)	4.57 (2.16; 1.04–16.8)	4.76 (2.41; 1.08–16.8)	4.39 (1.87; 1.04–7.29)	.34
PCR positivity with respiratory sample (≥1)	110/152 (72.4)	41 (68.3)	69 (75.0)	.37
PCR positivity with BAL	93/131 (71)	36 (70.6)	57 (71.3)	.94
BAL PCR value, mean (SD; range)	97235.4 (324 942.4; 132–1 645 414)	139 579.1 (417 435.7; 134–1 645 414)	66 100.3 (237 680.3; 132–1 352 255)	.40
PCR positivity with BAS	18/24 (75)	6 (60.0)	12 (85.7)	.15
BAS PCR value, mean (SD; range)	286 690.1 (743 974; 128–2 143 634)	358 896 (874 340.8; 154–2 143 634)	238 552.9 (695 922.6; 128–2 094 166)	.77
Serum GM positivity (≥0.5)	41/189 (21.7)	19 (21.4)	22 (22)	.91
Serum GM, mean (SD; range)	2.14 (2.13; 0.51–10.5)	2.82 (2.58; 0.51–10.50)	1.53 (1.42; 0.53–5.85)	.06
BDG positivity (≥80.0)	93/188 (49.5)	33 (36.7)	60 (61.2)	.001
BDG, mean (SD; range)	423.8 (355.4; 84.3–1802.9)	308.7 (225.1; 86–787)	487.2 (397.4; 84.3–1802.9)	.02
Histology	3/13 (23.1)	0 (0)	3 (42.9)	.07
Therapy (first line, also with switch)				
Voriconazole	160 (76.6)	81 (87.1)	79 (68.1)	.001
Isavuconazole	31 (14.8)	12 (12.9)	19 (16.4)	.48
L-Amb	18 (8.6)	0 (0)	18 (15.5)	<.001
Total duration of therapy, mean (SD; range), d	34.5 (43.9; 4–413)	32.4 (49.7; 4–413)	36.3 (38.5; 4–264)	.53
Outcomes				
LOS, mean (SD; range), d	55.6 (45.6; 8–276)	62.7 (52.1; 8–276)	49.9 (38.6; 8–189)	.04
Length of ICU stay, mean (SD; range), d	31.1 (29.5; 1–168)	36 (30.7; 2–168)	24.8 (26.8; 1–138)	.03
Clinical cure	95/204 (46.6)	45/91 (49.5)	50 (44.3)	.46
Relapse	5/204 (2.5)	2 (2.2)	3 (2.7)	.83
30-d Mortality	79/209 (37.8)	35 (37.6)	44 (37.9)	.96
90-d Mortality	105/209 (50.2)	42 (45.2)	63 (54.3)	.19

Abbreviations: BAL, bronchoalveolar lavage; BAS, bronchoaspirate; BDG, β-D-glucan; CAPA, coronavirus disease 2019–associated pulmonary aspergillosis; CCI, Charlson Comorbidity Index; CMV, cytomegalovirus; COPD, chronic obstructive pulmonary disease; CT, computed tomographic; GM, galactomannan; HIV, human immunodeficiency virus; ICU, intensive care unit; IMV, invasive mechanical ventilation; IPA, invasive pulmonary aspergillosis; L-Amb, liposomal amphotericin; LOS, length of hospital stay; SOFA, Sequential Organ Failure Assessment; PCR, polymerase chain reaction; PIPA, putative IPA.

[a]Data represent no. (%) of patients unless otherwise specified.

pulmonary disease (19.3% vs 30.7%; $P = .004$), solid cancer (14.6% vs 36.8%; $P < .001$), or liver cirrhosis (1.1% vs 12.3%; $P = .002$). Patients with PIPA were also more frequently coinfected with *Pneumocystis jirovecii* (1.2% vs 23.0% for CAPA; $P < .001$) and treated with noncorticosteroid immunosuppressive therapies (10.1% vs 26.1%; $P = .004$).

Symptoms did not differ between the groups, except for "recurrent fever,, which was more common in PIPA (3.2% vs 12.9%; $P = .01$). Radiological patterns of "ground glass" and "consolidation" were more often present among patients with CAPA (80.3% vs 48.2% for PIPA [$P < .001$] and 91.4% vs 77.7% [$P = .01$], respectively), and "tree in

bud" pattern among patients with PIPA (2.5% vs 20.5%; $P < .001$).

Almost half (47.4%) of the patients had a positive culture for *Aspergillus* species on ≥1 respiratory sample; the prevalent species was *A fumigatus* (62.8%), followed by *Aspergillus flavus* (18.6%), *Aspergillus terreus* (6.2%), *Aspergillus niger* (5.3%), and *Aspergillus nidulans* and *Aspergillus oryzae* (together 1.8%). On average, all species were susceptible to antifungal agents, except for *A oryzae* which showed a higher minimum inhibitory concentration for L-Amb and one strain of *A fumigatus* that was resistant to voriconazole and L-Amb (Supplementary Table 2).

When performed, BAL GM results were positive in 72.8% of cases (126 of 173), with a mean value of 4.57 (SD, 2.16; range, 1.04–16.8); positivity was more frequently observed among patients with CAPA (80.5% vs 66.7% for PIPA; $P = .04$), with similar mean values in PIPA and CAPA groups. There was a trend toward higher mean serum GM values among patients with CAPA (2.14 [SD, 2.13; range, 0.51–10.5] vs 1.53 [1.42; 0.53–5.85] for PIPA; $P = .06$).

PCR for *Aspergillus* was performed on ≥1 respiratory sample in 72.7% of patients (152 of 209): BAL samples in 131 patients (62.7%) and BAS samples in 24 (11.5%). For 3 patients, PCR results were available for both BAL and BAS samples. PCR results were positive in 110 of 152 patients (72.4%) for all respiratory samples, in 93 of 131 (71%) for BAL samples, and in 18 of 24 (75%) for BAS samples. There was a trend toward higher mean PCR values in patients with CAPA than in those with PIPA, in both BAL (139 579.1 [SD, 417 435.7; range, 134–165 414] vs 66 100.3 [237 680.3; 132–1 352 255], respectively; $P = .40$) and BAS (358 896 [874 340.8; 154–2 143 634] vs 238 552.9 [695 922.6; 128–2 094 166]; $P = .77$) samples. Patients with CAPA had significantly longer mean LOS (62.7 [SD, 52.1; range, 8–276] days vs 49.9 [38.6; 8–189] days for PIPA; $P = .04$) and ICU stays (36 [30.7; 2–168] days vs 24.8 [26.8; 1–138] days; $P = .03$) . No other differences in clinical outcomes, including clinical cure and overall mortality, were observed among the groups (Figure 1*A*).

Characteristics of Antifungal Treatments Among All Patients

Overall, voriconazole was the preferred first-line regimen, prescribed in 76% of the patients and significantly more frequently prescribed for those with CAPA (87.1% vs 68.1% for patients with PIPA; $P = .001$). For prescriptions of isavuconazole, no significant differences were observed between the groups. More patients with PIPA were treated with L-Amb (15.5% vs 0% for CAPA; $P < .001$) (Table 1).

Of the patients treated with voriconazole as a first-line regimen, 20 of 160 (12.5%) discontinued it (12 switched to isavuconazole); of those treated with L-Amb 10 of 18 (55.6%) changed to a second-line therapy; and of those treated with isavuconazole, only 3 of 31 (9.7%) switched to another regimen following clinician consideration (particularly for cost restrictions). Overall, drug-related AEs were registered in 17.7% of patients (3 of 18) receiving first-line treatment with L-Amb (the less-tolerated regimen), 7.8% (12 of 160) of receiving voriconazole, and none of those receiving isavuconazole (Supplementary Table 3).

Risk Factors Associated With Clinical Failure

Among all patients, 109 (53.4%) experienced clinical failure. Significant risk factors were CCI (OR, 1.21 [95% CI, 1.08–1.36]; $P = .001$), diabetes mellitus (2.17[.13–4.17]; $P = .02$), IMV (1.72 [.98–3.01]; $P = .06$), SOFA score (1.14 [1.01–1.28]; $P = .03$), positive serum BDG (2.41 [1.34–4.35]; $P = .003$), and treatment with voriconazole (1.83 [1.02–3.32]; $P = .04$) (Table 2 and Supplementary Table 4). Independent risk factors were CCI (OR, 1.30 [95% CI, 1.13–1.49]; $P < .001$) and IMV

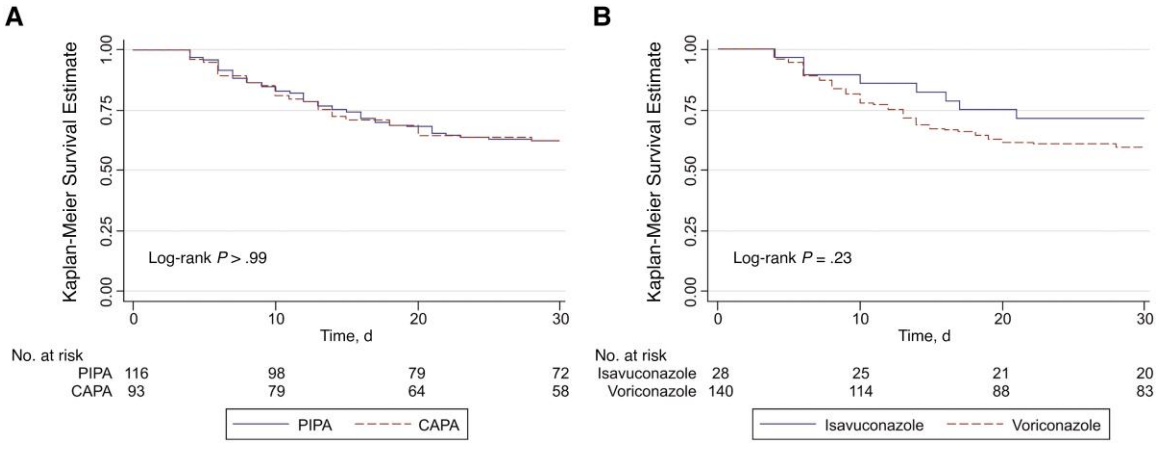

Figure 1. Kaplan-Meier survival curves after 30 days from the start of therapy of coronavirus disease 2019–associated pulmonary aspergillosis (CAPA) versus putative invasive pulmonary aspergillosis (PIPA) (*A*) and treatment with isavuconazole versus voriconazole (for patients who did not switch to a second-line regimen) (*B*).

(2.21 [1.15–4.25]; $P = .02$), but only the latter was confirmed after the PSM-adjusted analysis (2.24 [1.16–4.31]; $P = .02$). A trend toward the use of isavuconazole and clinical cure was observed with multivariate analysis (OR, 0.41 [95% CI, .16–1.02]; $P = .06$) and PSM-adjusted analysis (0.41 [.16–1.03]; $P = .06$) (Table 3).

Risk Factors for Overall 30-Day Mortality

Overall, patients who died within 30 days after the start of therapy, compared with survivors, had higher mean CCIs (5.7 [SD, 2.8; range, 0–14] vs 4.6 [2.4; 0–11], respectively; $P = .003$) and SOFA scores (6.1 [4.1; 1–17] vs 4.3 [2.9; 0–15]; $P = .009$); were more likely to have diabetes mellitus (37.3% vs 20.3%; $P = .008$), undergo IMV (61.3% vs 44.2%; $P = .02$), and have serum GM positivity (31% vs 16.1%; $P = .02$); and had higher copy numbers of *Aspergillus* (detected by PCR) in BAS samples (mean, 848 154.4 [SD, 1 160 159; range, 128–2 143 634] vs 5958 [9255.9; 237–28 971]; $P = .03$) (Table 2).

Risk factors for 30-day mortality included higher CCI (HR, 1.14 [95% CI, 1.05–1.24]; $P = .002$), diabetes mellitus (2.07 [1.29–3.30]; $P = .002$), liver cirrhosis (2.02 [1.01–4.06]), IMV (1.66 [1.04–2.63]; $P = .03$), SOFA score (1.09 [1.02–1.19]; $P = .02$), and positive serum GM result (1.79 [1.09–2.97]; $P = .02$) (Supplementary Table 4). Independent risk factors were IMV (HR, 3.96 [95% CI, 2.24–6.96]; $P < .001$) and serum GM positivity (HR, 1.76 [1.01–3.07]; $P = .046$). After PSM adjustment for age, IMV, and CCI, serum GM positivity was the only independent risk factor identified (HR, 1.78 [95% CI, 1.02–3.10]; $P = .04$) (Table 4).

Subgroup Analysis

The subgroup comparison between patients treated with voriconazole or isavuconazole only is reported in Supplementary Table 5. Isavuconazole was more often prescribed for cardiopathic patients. The mean total durations of treatment with voriconazole and isavuconazole were similar (29.6 [SD, 35.5; range, 4–264] and 27.9 [31.7; 1–89] days, respectively; $P = .91$). Isavuconazole was associated with higher rate of clinical cure (67.9% vs 41.6% for voriconazole; $P = .01$) and a trend toward less infection relapse (0% vs 1.5%; $P = .52$) and lower 30- and 90-day mortality rates (28.6% vs 40.7% [$P = .23$] and 39.3% vs 52.9%; [$P = .19$], respectively) (Figure 1*B* and Supplementary Table 6). The association between voriconazole use and clinical failure is shown in Figure 2.

DISCUSSION

Our study represents a large cohort of IPA in patients without hematological cancers, including >200 patients, half with CAPA and 30% were diagnosed outside the ICU. We found that patients with CAPA and those with PIPA present with different comorbid conditions and underlying conditions and selected mycological characteristics, but their outcomes are similar. The main risk factors were serum GM positivity for 30-day mortality and IMV for clinical failure. A trend toward the improved clinical cure with the use of isavuconazole was observed. In addition, subgroup analysis of patients who were initially treated with azole agents as the primary regimen, who did not experience any changes to their antifungal therapy during the treatment period, demonstrated that isavuconazole was associated with a higher clinical cure rate than voriconazole.

The characteristics of the included patients allowed us to outline the main epidemiological, clinical, and prognostic differences between these 2 distinct diseases: PIPA and CAPA. While the literature includes extensive investigations of IPA among critically ill and hematological patients, little is known about its clinical features in non-ICU and immunocompetent patients. The incidence of PIPA has steadily increased through the years, with incidence rates doubled in 2022 compared with 2020, while CAPA incidence peaked during 2021 and has decreased since . We believe that the increase in PIPA incidence results from several factors that have enhanced clinicians' knowledge and awareness of IPA.

First of all, in recent years, the definition of IPA has been updated or newly developed for different population. The modified-AspICU was elaborated in 2018 [5], the EORTC/MSG definitions were updated in 2019 [2], influenza-associated pulmonary aspergillosis was best defined in 2020 [14], and the CAPA definition was first published at the end of the same year [8]. More recently, the FUNDICU consensus document introduced new definitions for IPA in nonneutropenic adult ICU patients, a highly heterogeneous population with a broad range of baseline comorbid and predisposing conditions [15]. However, the fact that a significant percentage of PIPA cases in our study could not be classified according to the EORTC/MSG or modified-AspICU definitions highlights that the current algorithms still have limitations and need further refinement to make them more broadly applicable, as already reported in literature [16, 17].

A second factor contributing to the increase in PIPA incidence is the heightened focus and interest in IPA following the COVID-19 pandemic and the establishment of the CAPA definition. Finally, inclusion of new biomarkers such as *Aspergillus* PCR in diagnostic definition (not as exclusive mycological criteria) may have enhanced efficiency in IPA diagnosis, although the performance in nonneutropenic, critically ill patients is still debated [15, 18–20].

Aspergillus PCR has been available at our center since 2017 and it was performed on respiratory samples in a considerable percentage of patients included in our study, with high positivity rates with both BAL and BAS samples. Although the difference was not statistically significant, the average PCR value tended to be higher in patients with CAPA than in those with

Table 2. Characteristics of Patients With or Without Clinical Failure or 30-Day Mortality

Characteristic, Treatment, or Outcome	Patients by Clinical Failure, No. (%)[a]			Patients by 30-d Mortality, No. (%)[a]		
	Yes (n = 109/209 [53.4%])	No (n = 95/209 [46.6%])	*P* Value	Yes (n = 79/209[37.8%])	No (n = 130/209 [62.2%])	*P* Value
Age, mean (SD; range), y	68.6 (10.4; 41–90)	66.0 (13.9; 23–94)	.13	68.8 (10.0; 41–90)	66.8 (13.4; 23–94)	.17
Male sex	77 (70.6)	56 (58.9)	.08	56 (70.9)	81 (62.3)	.21
Ward of diagnosis						
ICU	77 (70.6)	64 (67.4)	.61	59 (74.7)	85 (65.4)	.16
Medical	32 (29.4)	31 (32.6)	.61	20 (25.3)	44 (33.9)	.20
Surgical	0 (0)	0 (0)	…	0 (0)	1 (0.8)	.44
Year of diagnosis						
2018	6 (5.5)	7 (7.4)	.38	5 (6.3)	10 (7.7)	.35
2019	16 (14.7)	4 (4.2)	.01	12 (15.2)	8 (6.2)	.03
2020	25 (22.9)	19 (20.0)	.61	20 (25.3)	26 (20.0)	.37
2021	36 (33.0)	44 (46.3)	.052	23 (29.1)	58 (44.6)	.03
2022	26 (23.8)	21 (22.1)	.77	19 (24.1)	28 (21.5)	.67
Time from admission to IPA, mean (SD; range), d	19.7 (16.7; 1–198)	21.8 (21.6; 1–129)	.45	19.9 (17.5; 1–98)	21.1 (19.8; 1–129)	.65
Comorbid conditions						
CCI, mean (SD; range)	5.6 (0.3; 0–14)	4.4 (0.2; 0–11)	<.001	5.7 (2.8; 0–14)	4.6 (2.4; 0–11)	.003
Heart disease	30 (28.9)	27 (28.4)	.95	21 (28)	37 (28.9)	.89
Hypertension	69 (65.7)	56 (59.6)	.37	47 (61.8)	80 (62.9)	.87
Vasculopathy	21 (20.2)	21 (22.1)	.74	16 (21.3)	27 (21.1)	.97
Neurological disease	16 (15.4)	9 (9.5)	.21	9 (12)	16 (12.5)	.92
Diabetes mellitus	35 (33.7)	18 (18.9)	.02	28 (37.3)	26 (20.3)	.008
Dyslipidemia	30 (28.9)	27 (28.4)	.95	25 (33.3)	32 (25.0)	.20
Renal failure	12 (11.5)	15 (15.8)	.38	10 (13.3)	17 (13.3)	.99
COPD	24 (23.1)	22 (23.2)	.99	15 (20)	32 (25.0)	.42
Other pneumopathy	16 (15.2)	14 (14.7)	.92	13 (17.1)	19 (14.8)	.67
Previous tuberculosis	2 (1.9)	4 (4.2)	.35	1 (1.3)	5 (3.9)	.30
Solid cancer	31 (29.8)	22 (23.2)	.29	24 (32)	31 (24.2)	.23
HIV	1 (0.9)	1 (1.1)	.95	1 (1.3)	1 (0.8)	.70
Solid organ transplant	8 (7.7)	10 (10.5)	.49	5 (6.7)	13 (10.2)	.40
Liver cirrhosis	10 (9.5)	4 (4.2)	.14	9 (11.8)	6 (4.7)	.06
Other liver disease	11 (10.6)	8 (8.4)	.60	8 (10.7)	11 (8.6)	.62
Autoimmune disease	11 (10.6)	10 (10.5)	.99	8 (10.7)	14 (10.9)	.95
Active smoker status	18 (17.7)	13 (13.8)	.42	10 (13.7)	23 (18.1)	.69
Concomitant COVID-19	46 (42.2)	45 (47.4)	.46	35 (44.3)	58 (44.6)	.96
Concomitant influenza	1 (0.9)	2 (2.1)	.48	1 (1.3)	2 (1.5)	.87
Extrinsic factors						
IMV	60 (57.7)	42 (44.2)	.06	46 (61.3)	57 (44.2)	.02
Steroids	71 (66.4)	70 (73.7)	.26	53 (68.8)	90 (69.2)	.95
Steroid duration >3 wk	28 (28.3)	32 (34.4)	.36	19 (27.1)	41 (32.8)	.38
Other immunosuppressive therapies	18 (17.3)	21 (22.1)	.39	14 (18.7)	25 (19.4)	.90

Table 2. Continued

Characteristic, Treatment, or Outcome	Patients by Clinical Failure, No. (%)[a]			Patients by 30-d Mortality, No. (%)[a]		
	Yes (n = 109/209 [53.4%])	No (n = 95/209 [46.6%])	*P* Value	Yes (n = 79/209[37.8%])	No (n = 130/209 [62.2%])	*P* Value
Tocilizumab	22 (21.6)	32 (34.0)	.051	36 (28.8)	18 (23.7)	.43
Active chemotherapy	11 (10.7)	7 (7.4)	.42	6 (8.0)	12 (9.4)	.74
Concomitant antibiotic therapy	93 (88.6)	76 (84.4)	.40	67 (88.2)	106 (86.2)	.69
Coinfection on respiratory sample						
CMV	25 (24.0)	22 (24.2)	.98	20 (26.7)	28 (22.8)	.53
Pneumocystis jirovecii	15 (14.4)	12 (13.3)	.83	13 (17.3)	14 (11.4)	.24
Pseudomonas aeruginosa	23 (21.7)	14 (15.6)	.27	16 (20.8)	23 (18.7)	.72
Clinical presentation						
SOFA, mean (SD; range)	5.8 (4.2; 0–17)	4.2 (2.4; 0.11)	.02	6.1 (4.1; 1–17)	4.3 (2.9; 0–15)	.009
Septic shock	18 (18.6)	15 (15.9)	.64	10 (14.3)	23 (18.3)	.48
Hemoptysis	3 (2.8)	2 (2.1)	.77	2 (2.5)	5 (3.9)	.61
Worsening respiratory insufficiency	90 (82.6)	75 (78.9)	.51	68 (86.1)	100 (76.9)	.11
Dyspnea	77 (70.6)	63 (66.3)	.51	56 (70.9)	88 (67.7)	.63
Persistent fever	7 (6.4)	12 (12.6)	.13	7 (8.9)	12 (9.2)	.93
Recurrent fever	8 (7.3)	10 (10.5)	.42	4 (5.1)	14 (10.8)	.15
Chest pain	0 (0)	3 (3.2)	.06	0 (0)	3 (2.3)	.17
Pleural friction rub	0 (0)	1 (1.1)	.28	0 (0)	1 (0.8)	.44
Tracheobronchial pseudomembranes/ ulcerations	1 (0.9)	2 (2.1)	.48	1 (1.3)	2 (1.55)	.87
CT findings						
Cavitation	13 (13.4)	15 (16.5)	.55	9 (13.2)	19 (15.2)	.71
Ground glass	60 (61.9)	57 (62.6)	.91	42 (61.8)	77 (61.6)	.98
Consolidation	78 (80.4)	79 (86.8)	.24	55 (80.9)	106 (84.8)	.48
Nodules	31 (31.9)	31 (34.1)	.76	20 (29.4)	42 (33.6)	.55
Tree in bud	15 (15.5)	10 (10.9)	.37	7 (10.3)	18 (14.4)	.42
Halo sign	3 (3.1)	3 (3.3)	.94	3 (4.4)	3 (2.4)	.44
Air crescent sign	0 (0)	0 (0)	…	0 (0)	0 (0)	…
Microbiology						
Culture positive with respiratory sample (≥1)	48/109 (44.0)	47/95 (49.5)	.44	39/77 (50.6)	59/130 (45.4)	.46
Microscopy on BAL	5/96 (5.2)	8/84 (9.5)	.26	4/69 (5.8)	11/115 (9.5)	.37
BAL GM positivity (≥1.0)	65/91 (71.4)	59/78 (75.6)	.54	44/65 (67.7)	82/108 (75.9)	.24
BAL GM, mean (SD; mean)	4.28 (1.77; 1.04–7.29)	4.85(2.50; 1.12–16.8)	.14	4.2 (1.6; 1.0–6.8)	3.5 (2.6; 1.1–7.3)	.18
PCR positivity with respiratory sample (≥1)	51/74 (68.9)	58/77 (75.3)	.45	32/48 (66.7)	78/104 (75.0)	.29
PCR positivity with BAL	43/63 (68.2)	49/66 (74.2)	.45	29/44 (65.9)	64/87 (73.6)	.36
BAL PCR value, mean (SD; range)	86 103.8 (282 715.3;132–1 387 200)	105 420 (356 771.4; 134–1 645 414)	.82	117116.3 (330424.2; 262–1387200)	88 507 (326 258.3; 132–1 645 414)	.76
PCR positivity with BAS	9/12 (75.0)	9/12 (75.0)	>.99	6/7 (85.7)	12/17 (70.6)	.44
BAS PCR value, mean (SD; range)	534 177.6 (978 248.1; 128–2 143 634)	3847.3 (5419; 237–15 235)	.18	848 154.4 (1 160 159; 128–2 143 634)	5958 (9255.9; 237–28 971)	.03
Serum GM positivity (≥0.5)	26/99 (26.3)	14/87 (16.1)	.09	22/71 (31)	19/118 (16.1)	.02
Serum GM, mean (SD; range)	2.02 (1.78; 0.56–5.85)	2.37 (2.72; 0.51–10.5)	.63	2.2 (1.8; 0.6–5.8)	2.0 (2.4 ;0.5–10.5)	.75

Table 2. Continued

Characteristic, Treatment, or Outcome	Patients by Clinical Failure, No. (%)[a]		*P* Value	Patients by 30-d Mortality, No. (%)[a]		*P* Value
	Yes (n = 109/209 [53.4%])	No (n = 95/209 [46.6%])		Yes (n = 79/209[37.8%])	No (n = 130/209 [62.2%])	
BDG positivity (≥80.0)	59/99 (59.6)	33/87 (37.9)	.003	42/72 (58.3)	51/116 (43.9)	.055
BDG, mean (SD; range)	405.4 (325.9; 84.3–1623)	466.7 (405.8; 95.6–1802.9)	.43	423.6 (344.7; 96.5–1623)	424.0 (367.2; 84.3–1802.9)	>.99
Histology	3/8 (37.5)	0/0 (0.0)	.12	1/4 (25)	2/9 (22.2)	.91
Diagnosis						
CAPA	46 (42.2)	45 (47.4)	.46	35 (44.3)	58 (44.6)	.96
PIPA	63 (57.8)	50 (52.6)	.46	44 (55.7)	72 (55.4)	.96
Therapy						
Voriconazole (1st line)	89 (81.7)	67 (70.5)	.06	64 (81)	96 (73.9)	.24
Isavuconazole (1st line)	11 (10.1)	20 (21.1)	.03	9 (11.4)	22 (16.9)	.28
L-Amb (1st line)	9 (8.3)	8 (8.4)	.97	6 (7.6)	12 (9.2)	.68
Voriconazole (sole treatment, without switch)	80 (73.4)	57 (60.0)	.04	57 (72.2)	83 (63.8)	.22
Isavuconazole (sole treatment, without switch)	9 (8.3)	19 (20.0)	.02	8 (10.1)	20 (15.4)	.28
Total duration of therapy, mean (SD; range), d	19.7 (18.3; 4–114)	51.0 (56.9; 4–413)	<.001	11.5 (5.8; 4–28)	48.4 (50.6; 4–413)	<.001
Outcomes						
LOS, mean (SD; range) d	40.9 (27.9; 8–172)	74.0 (55.5; 11–276)	<.001	31.8 (18.8; 8–107)	70.6 (50.7; 8–276)	<.001
Length of ICU stay, mean (SD; range), d	27.3 (25.9; 1–68)	35.4 (32.7; 1–138)	.12	20.9 (13.9; 1–70)	38.2 (34.9; 1–168)	.001

Abbreviations: BAL, bronchoalveolar lavage; BAS, bronchoaspirate; BDG, β-D-glucan; CAPA, COVID-19–associated pulmonary aspergillosis; CCI, Charlson Comorbidity Index; CMV, cytomegalovirus; COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease 2019; CT, computed tomographic; GM, galactomannan; HIV, human immunodeficiency virus; ICU, intensive care unit; IMV, invasive mechanical ventilation; IPA, invasive pulmonary aspergillosis; L-Amb, liposomal amphotericin; LOS, length of hospital stay; PCR, polymerase chain reaction; PIPA, putative IPA; SOFA, Sequential Organ Failure Assessment.

[a]Data represent no. (%) of patients unless otherwise specified.

Table 3. Multivariate Analysis of Risk Factors for Clinical Failure With Unadjusted and Adjusted Odds Ratios

Risk Factor	Unadjusted OR (95% CI)	*P* Value	Adjusted OR[a] (95% CI)	*P* Value
Age	1.01 (.97–1.03)	.65	1.01 (.98–1.04)	.53
CCI	1.30 (1.13–1.49)	<.001[b]	0.98 (.45–2.19)	.98
IMV	2.21 (1.15–4.25)	.02[b]	2.24 (1.16–4.31)	.02[b]
Isavuconazole[c]	0.41 (.16–1.02)	.06	0.40 (.16–1.03)	.06

Abbreviations: CCI, Charlson Comorbidity Index; CI, confidence interval; ICU, intensive care unit; IMV, invasive mechanical ventilation; OR, odds ratio.

[a]ORs adjusted for CCI and ICU admission.

[b]Significant at $P < .05$.

[c]Sole treatment, without switch.

Table 4. Multivariate Analysis of Risk Factors for 30-Day Mortality With Unadjusted and Adjusted Hazard Ratios

Risk Factor	Unadjusted HR (95% CI)	*P* Value	Adjusted HR[a] (95% CI)	*P* Value
Age	1.02 (.99–1.04)	.20	1.02 (.99–1.08)	.19
Male sex	1.46 (.81–2.61)	.20	1.51 (.84–2.70)	.17
LOS	0.95 (.93–.97)	<.001[b]	0.95 (.93–.97)	<.001[b]
CCI	1.04 (.93–1.17)	.47	1.52 (.50–4.64)	.46
IMV	3.96 (2.24–6.98)	<.001[b]	22.24 (.14–3581.20)	.23
Liver cirrhosis	1.93 (.78–4.78)	.16	1.86 (.74–4.65)	.18
Serum GM positivity	1.76 (1.01–3.07)	.046[b]	1.78 (1.02–3.10)	.04[b]

Abbreviations: CCI, Charlson Comorbidity Index; CI, confidence interval; GM, galactomannan; HR, hazard ratio; IMV, invasive mechanical ventilation; LOS, length of hospital stay.

[a]Adjusted for age, IMV, and CCI.

[b]Significant at $P < .05$.

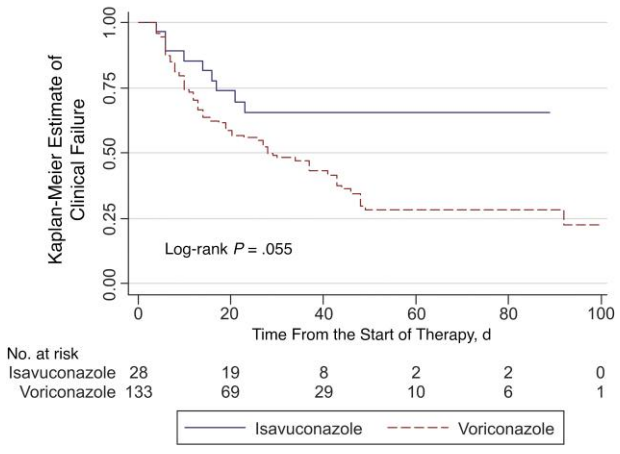

Figure 2. Kaplan-Meier curve of occurrence of clinical failure between patients treated only with voriconazole or isavuconazole (without switching to a second-line regimen).

PIPA, in a concordant manner with both BAL and BAS samples. Moreover, the positivity rate of *Aspergillus* PCR is also in line with results of BAL GM, already a well-recognized diagnostic criterion for IPA [21, 22]. Therefore, *Aspergillus* PCR could be useful in diagnosing IPA, even from nonbronchoscopic lavage samples when BAL cannot be sampled. Further analyses are needed to confirm this assumption.

Beyond the difference in average PCR value, patients with CAPA also had higher rates of BAL GM positivity and higher mean serum GM values than patients with PIPA. These findings suggest a possible greater fungal disease load in patients with CAPA [23], favored by COVID-19 damage to respiratory epithelium, immune response dysregulation, cytokine storm, and hyperinflammation, as reported elsewhere [24]. In contrast, typical radiological features and symptoms (such as cavitation, nodules, or halo sign but also hemoptysis and chest pain) are less common in nonneutropenic patients, especially when there is an overlap with other infections [25]. The literature shows typical radiological findings in 28.8% of patients with PIPA [6] and 17.6% of those with CAPA [24].

Another difference in mycological markers between the 2 groups was the higher positivity rate and higher mean value of BDG among patients with PIPA, compared with the CAPA group. While BDG is primarily used for its negative predictive value, elevated levels can increase suspicion of a fungal infection that warrants further investigations, particularly in the absence of known confounding factors (eg, β-lactam therapy, surgery or other recognized influences) [26, 27]. This finding could be especially relevant for patients admitted to non-ICU wards (such as patients with PIPA in our study), where deep respiratory samples (BAL or BAS) may not be readily available.

Our analysis highlights, in line with the literature [3, 28–30], that patients with PIPA had more comorbid conditions than those with CAPA: higher CCIs and more COPD, solid cancer, and liver cirrhosis. This result seems to suggest that, in the CAPA group, COVID-19 itself and concurrent COVID-19 treatments (corticosteroids and immunomodulators) are the predominant predisposing factors for aspergillosis development. Feys et al [10] demonstrated that ICU admission in the vaccination era was independently associated with CAPA development, suggesting the need to consider antifungal prophylaxis in critically ill patients with COVID-19 requiring mechanical ventilation and high doses of corticosteroids.

In the current study, 30- and 90-day mortality rates were similar to those previously reported in literature. Cornillet et al [31] compared mortality rates between nonneutropenic and neutropenic patients, reporting rates of 89% and 60%, respectively. They hypothesized that this difference was related to a lower level of suspicion and monitoring for aspergillosis in nonneutropenic patients, leading to poorer management and a delay in

the initiation of therapy. In addition, Meersseman et al [32] observed a mortality rate of 91% among ICU patients without cancer. However, while Feys et al [10] found higher 90-day mortality rates in patients with CAPA than in those without (48% vs 21%, respectively), we observed no differences in mortality rates between the CAPA and PIPA groups.

This difference may be explained by all diagnoses in our study being approved by an infectious diseases consultant, who limited misdiagnosis or inclusion of colonized patients. Misdiagnosis or inclusion of colonized patients may occur more frequently in association with PIPA due to a lack of validated diagnostic definitions in nonneutropenic patients. Another reason for this difference may be the independent role of patient management and therapies. Indeed, the study cohort reported by Feys et al [10] included only patients who underwent IMV, and only 70% of our patients with CAPA underwent IMV. Furthermore, Feys et al used the EORTC/MSG host criteria for patient selection, which may have led to the inclusion of some more hematologically fragile patients, who were excluded from our cohort. Finally, they found that azoles were the preferred drugs used, but they did not distinguish antifungal therapies in detail [10].

Another important and novel finding of our study is the confirmation of the independent prognostic role of serum GM in predicting 30-day mortality, even in nonhematological patients [33].

Importantly, isavuconazole in our cohort tended to be associated with better clinical cure than voriconazole, also when adjusted for age, comorbid conditions, and severity of clinical presentation. Randomized prospective clinical comparative trials are lacking, but several retrospective studies reported similar efficacy and improved safety between isavuconazole and voriconazole [34–36]. The most marked difference in clinical failure between isavuconazole and voriconazole was observed during the first month of treatment (as shown with Kaplan-Meier curves), highlighting the importance of early appropriate management.

Moreover, in line with the SECURE trial, there were fewer AEs in patients treated with isavuconazole. In the post hoc analysis of the VITAL and SECURE trials [11], considering patients treated with isavuconazole, the authors concluded that AEs were more frequent and more severe in the ≥65-year-old subgroup than in the <65-year-old subgroup and that outcomes were basically worst in the older patient group (higher mortality rate and lower overall, clinical, microbiological and radiological response). However, the post hoc analyses also noted a more favorable safety profile for isavuconazole than for voriconazole, including in the subgroup of younger patients, due to less frequent hepatotoxicity [11].

In our study, the overall mean age of the patients treated with isavuconazole was higher than that reported in other studies, suggesting a good safety profile in older patients. It is important to note that, at our university hospital, we began performing therapeutic drug monitoring not only for voriconazole but also for isavuconazole in selected patients during the last year of the study. Unfortunately, we were unable to retrieve the therapeutic drug monitoring results for this study as they were performed at another hospital and were not available in the electronic medical records. Although the evidence remains uncertain [37], we believe that the absence of AEs in our population could serve a proof of concept for the necessity of therapeutic drug monitoring for isavuconazole, at least for elderly patients to prevent toxicity.

Finally, a trend toward isavuconazole with lower mortality and IPA infection relapse rates was observed. Considering the good tolerability and improved outcomes associated with isavuconazole observed in our study, this drug could be considered the optimal therapeutic choice for elderly patients and those hospitalized with multiple comorbid conditions. Due to the monocentric retrospective nature of the study, these results need to be confirmed in future randomized controlled trials.

Our study has some limitations. First, sample sizes were relatively small for subanalyses of age and treatment groups and analyzed risk factors for clinical failure and 30-day mortality. Second, unmatched analyses were susceptible to confounding factors, though, to limit the indication biases, PS weighting was adopted to account for the imbalance in antifungal treatment allocation. Finally, criteria for diagnosing probable aspergillosis in nonhematological patients have not been extensively validated. To overcome this general limitation, we enrolled only patients treated in agreement with the hospital's infectious diseases consultant.

In conclusion, we show that IPA has a different presentation in patients with COVID-19 than in those without it, with a higher grade of fungal burden in the CAPA group, which does not translate into any differences in outcomes. Treatment with isavuconazole seems to be associated with better clinical cure and optimal safety profile, but due to the retrospective nature of our study, our data need to be confirmed by further prospective multicenter studies. Finally, serum GM was confirmed to be a predictor of mortality risk, even in nonhematological patients.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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