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Research article

Factors affecting mortality in COVID-19-associated pulmonary aspergillosis: An international ID-IRI study

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ABSTRACT

Background: This study aimed to identify factors that influence the mortality rate of patients with coronavirus disease (COVID-19)-associated pulmonary aspergillosis (CAPA).
Methods: In this cross-sectional study, data from 23 centers across 15 countries, spanning the period of March 2020 to December 2021, were retrospectively collected. The study population comprised patients who developed invasive pulmonary aspergillosis while being treated for COVID-19 in the intensive care unit. Cox regression and decision tree analyses were used to identify factors associated with mortality in patients with CAPA.
Results: A total of 162 patients (males, 65.4 %; median age: 64 [25th–75th: 54.0–73.8] years) were included in the study, of whom 113 died during the 90-day follow-up period. The median duration from CAPA diagnosis to death was 12 (25th–75th: 7–19) days. In the multivariable Cox regression model, an age of ≥65 years (hazard ratio [HR]: 2.05, 95 % confidence interval [CI]: 1.37–3.07), requiring vasopressor therapy at the time of CAPA diagnosis (HR: 1.80, 95 % CI: 1.17–2.76), and receiving renal replacement therapy at the time of CAPA diagnosis (HR: 2.27, 95 % CI: 1.35–3.82) were identified as predictors of mortality. Decision tree analysis revealed that patients with CAPA aged ≥65 years who received corticosteroid treatment for COVID-19 displayed higher mortality rates (estimated rate: 1.6, observed in 46 % of patients).
Conclusion: This study concluded that elderly patients with CAPA who receive corticosteroids are at a significantly higher risk of mortality, particularly if they experience multiorgan failure.

1. Introduction

At the end of 2019, a novel coronavirus—severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) that caused the coronavirus disease (COVID-19)—was identified, leading to a global pandemic [1]. Immunocompromised states—such as prolonged severe neutropenia, allogeneic hematopoietic stem cell transplantation (HSCT), solid organ transplantation (SOT), inherited or acquired immunodeficiency, long-term corticosteroid use, and underlying lung damage—predispose individuals to invasive pulmonary aspergillosis (IPA) [2,3]. However, the incidence of aspergillosis has increased with the emergence of severe viral pulmonary illnesses, such as influenza and COVID-19. COVID-19-associated pulmonary aspergillosis (CAPA) is induced by an IPA-overlapping influenza infection [4,5]. Epithelial destruction, downregulated expression of several genes encoding proteins with functions in the opsonization, recognition, and killing of conidia, and lower neutrophil fractions predispose patients with COVID-19 and influenza to aspergillosis [6]. Furthermore, the use of glucocorticoids or monoclonal antibodies such as tocilizumab has been found to be associated with the development of CAPA [7].

The prevalence of CAPA among patients in the intensive care unit (ICU) is approximately 10 %, and the mortality rate is high [8,9]. Numerous studies have investigated the risk factors for CAPA development and the impact of CAPA on mortality by comparing patients with COVID-19 with and without IPA [10–15]. However, despite alarming mortality rates, information regarding the factors influencing mortality among patients with CAPA is scarce. Therefore, the objective of this study was to identify the predisposing factors, clinical features, and outcomes that contribute to mortality in this specific group of patients through collaborative efforts on an international scale. To the best of our knowledge, this study represents one of the most extensive and comprehensive international case series of CAPA reported thus far and is the largest study to date to examine the predictors of mortality in this population.

2. Methods

2.1. Study design and setting

This cross-sectional study used data of aspergillosis cases in patients with COVID-19 who received treatment between March 2020 and December 2021. Data were gathered retrospectively from 23 medical facilities spanning 15 countries: Bahrain, Bangladesh, Belgium, Croatia, the Czech Republic, Egypt, Hungary, Iran, Italy, Jordan, Qatar, Romania, Russia, Slovakia, and Turkey. No sample size calculation was performed before the study. We aimed to include all eligible patients from the participating centers during the defined study period.

2.2. Data collection

The study protocol, including case definitions and the inclusion and exclusion criteria, was prepared and shared with the centers. The centers were then asked to send the information of all patients diagnosed with CAPA within the study period (March 2020 and December 2021). Subsequently, the centers submitted data for patients who satisfied the defined case parameters through a dedicated webpage link hosted on Microsoft Forms. The data were submitted between December 2021 and April 2022. To increase data quality and standardization, any inaccurate data on diagnostic criteria or false data entries were communicated to the participating centers.

Patient data on demographics, comorbidities, and predisposing factors were collected, including diabetes mellitus, cardiovascular diseases, chronic kidney disease, chronic respiratory illness, active malignancy, HSCT, SOT, steroid (prednisolone, ≥20 mg/day for ≥4 weeks) or immunosuppressive therapy in the 3 months prior, clinical features, treatment for COVID-19 (including antiviral, glucocorticoid, and immunosuppressive therapies), the time interval between the initial symptom of COVID-19 to aspergillosis, site involvement (pulmonary with or without tracheobronchitis and sinusitis), signs on chest computed tomography (CT), microbiological findings, histopathological evidence, details of antifungal treatment (antifungal medication and duration of therapy), and mortality.

2.3. Case definition

The diagnosis of COVID-19 was confirmed using a reverse transcription polymerase chain reaction (RT-PCR) test that detects SARS-CoV-2 RNA in respiratory specimens. The diagnosis of CAPA was based on established diagnostic criteria that were previously published. CAPA diagnosis was categorized as possible, probable, or proven depending on the validity of the samples and level of diagnostic certainty [4]. The diagnostic criteria encompassed clinical, radiological, pathological, and/or mycological criteria considering host factors. A case definition based on the inclusion criteria is shown in Fig. 1.

a) Host factors for the diagnosis of CAPA included the presence of acute respiratory distress syndrome after COVID-19 requiring ICU admission.
b) Clinical criteria included refractory fever, deterioration of respiratory symptoms, or tracheobronchial aspergillosis on bronchoscopy. Refractory fever refers to a fever that persists for >3 days, or a new fever that occurs after a period of defervescence lasting >48 h during appropriate antibiotic therapy in the absence of any other apparent cause. The tracheobronchial form of aspergillosis was defined as one of the following findings observed during bronchoscopic analysis: tracheobronchial ulceration, nodule, pseudomembrane, plaque, or eschar.

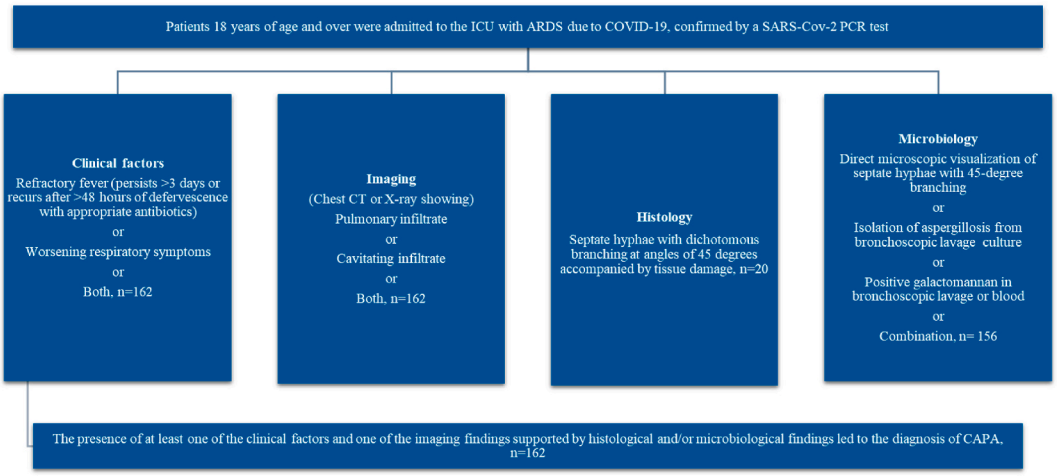

Fig. 1. An overview of the study's case definition and inclusion criteria.
ARDS, acute respiratory distress syndrome; CT, computed tomography; ICU, intensive care unit; PCR, polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus-2.

c) All patients underwent chest CT or radiography to confirm involvement compatible with aspergillosis.
d) Histopathological diagnosis was based on the presence of septate hyphae with dichotomous branching at 45° angles, accompanied by tissue damage.
e) Microbiological diagnosis was based on direct microscopic visualization of septate hyphae with dichotomous branching at angles of 45°, isolation of *Aspergillus* in a bronchoscopic lavage culture, or detection of positive galactomannan (GM) in bronchoscopic lavage or blood with validated cutoff values recommended by the guidelines.

2.4. Statistical analysis

Normality was assessed using histograms and the Shapiro-Wilk test. Continuous variables were summarized as median with 25th–75th percentile. Pearson's Chi-squared test or Fisher's exact test was used to compare categorical variables between the surviving and nonsurviving groups. Sequential Organ Failure Assessment (SOFA) scores were compared using the Mann–Whitney *U* test. Survival probabilities were estimated using the Kaplan–Meier method with right-censored data on the 90th day from CAPA diagnosis. We used the least absolute shrinkage and selection operator (LASSO) algorithm for the Cox model to select potential variables that could affect mortality. A total of 21 variables (age, sex, diabetes mellitus, hypertension, obesity, chronic obstructive pulmonary disease, malignancy, chronic renal failure, chronic heart disease, HSCT or SOT, immunosuppressive therapy prior to COVID-19, antiviral treatment, corticosteroids used for COVID-19, monoclonal antibody drug used for COVID-19, broad-spectrum antimicrobial use prior to CAPA, invasive mechanical ventilation prior to CAPA, site of aspergillosis involvement, SOFA score, invasive mechanical ventilation at the time of CAPA diagnosis, vasopressor need, and renal replacement therapy [RRT] at the time of CAPA diagnosis) were added to LASSO variable selection. The optimal regularization parameter (λ) was estimated by 10-fold cross-validation. Prior to the selection procedure, missing SOFA scores (10 observations) were imputed using a predictive mean-matching method.

With LASSO-selected variables, hazard ratios (HRs) with their 95 % confidence intervals (CI) were estimated using univariate and multivariate Cox regression models. Finally, we applied Cox model recursive partitioning and regression tree analysis with LASSO-selected variables using the rpart function in the "rpart" package. Double-sided p-values <0.05 were considered significant. Statistical analysis and visualization were performed using R version 4.3.1 (R Foundation for Statistical Computing, Vienna, Austria).

3. Results

3.1. Characteristics of patients with CAPA

A total of 162 patients (males: 65.4 %, median age: 64 [25th–75th: 54.0–73.8] years) with CAPA were identified during the 20-month COVID-19 pandemic. All patients were admitted to ICU. There was at least one comorbid condition in 88.3 % of patients (n = 143), 15.4 % (n = 25) received immunosuppressive therapy, and 3.1 % (n = 5) underwent HSCT or SOT.

Table 1
Radiological and microbiological data of patients with CAPA (n = 162).

	n (%)
Findings on chest computed tomography for aspergillosis	
Wedge-shaped and segmental or lobar consolidation	81 (50.0 %)
Cavitated nodules	19 (11.7 %)
Cavity	14 (8.64 %)
Air crescent sign	14 (8.64 %)
Dense, well-circumscribed lesions(s) with or without a halo sign	34 (21.0 %)
Site of involvement of aspergillosis:	
Only pulmonary	138 (85.2 %)
Tracheobalitis and pulmonary	24 (14.8 %)
Aspergillus spp. isolation in respiratory samples	102 (63.0 %)
Type of the sample that *Aspergillus* spp. isolated, n = 102	
Bronchoscopic lavage	36 (22.2 %)
Endotracheal aspirate	66 (40.74 %)
Species of *Aspergillus* isolated, n = 102	
A. fumigatus (n = 35, 39.3 %)	35 34.3 %)
A. terreus	22 (21.6 %)
A. nigar	18 (17.6 %)
Other species of *Aspergillus*	27 (26.5 %)
Serology of *Aspergillus* spp.	
Bronchoscopic lavage galactomannan (index≥1.0)	44 (93.6 %)
Serum galactomannan (index≥0.5)	69 (80.2 %)
Serum beta-D-glucan (>80 pg/mL)	9 (37.5 %)
Classification of CAPA:	
Proven	20 (12.3 %)
Probable	102 (63.0 %)
Possible	40 (24.7 %)

CAPA, coronavirus disease (COVID-19)-associated pulmonary aspergillosis.

3.2. Data on diagnosis

Radiological and microbiological data are presented in Table 1. Wedge shape and segmental or lobar consolidation were the most observed radiological appearances on CT (50.0 %). Tracheobronchitis with pulmonary involvement was present in 14.8 % of patients (n = 24). We isolated *Aspergillus* in 102 patients (63.0 %), and the most frequent isolate was *A. fumigatus* (n = 35, 34.3 %). Of the patients who underwent serology, 93.6 % (n = 44) had a positive bronchoscopic lavage GM (index ≥1.0).

3.3. Data on therapy

A total of 122 (75.3 %) patients received antiviral therapy for COVID-19. Favipiravir, remdesivir, hydroxychloroquine, molnupiravir, and lopinavir/ritonavir were used in 30.2 %, 30.2 %, 8 %, 6.2 %, and 0.6 % of the patients, respectively. Of the 162 patients, 152 (93.8 %) received corticosteroids and 47.5 % (77/162) received monoclonal antibodies (IL-1 receptor antibody, 13.6 % [n = 22]; IL-6 receptor antibodies, 37 % [n = 60]) for the treatment of COVID-19. Almost all patients received antifungal therapy for aspergillosis (98.1 %, n = 159). Among these, voriconazole and other antifungal therapies were administered to 54.1 % (86/159) of the patients, followed by echinocandins and other antifungal therapies (33.3 %, 53/159), and amphotericin B and other antifungal therapies (16.4 %, 26/159).

3.4. Clinical outcomes

A total of 113 (69.7 %) patients deceased within the 90-day follow-up. The 30-day probability of survival was 40.1 % (Fig. 2). The median duration from CAPA diagnosis to death was 12 (25th–75th: 7–19) days. Table 2 shows a comparison of the demographic variables and treatments received for COVID-19 prior to CAPA diagnosis among patients who survived and died. Mortality was more common in patients with than without hypertension (84.6 % vs. 62.7 %, p = 0.008). Additionally, mortality was higher in patients who used broad-spectrum antimicrobials before CAPA (74.2 % vs. 52.9 %, p = 0.028).

A comparison of radiological involvement and clinical variables at the time of CAPA diagnosis between patients who survived and those who died is presented in Table 3. The mortality rate was 91.7 % in patients with tracheobronchitis and pulmonary involvement (p = 0.022). Mortality was higher in those who required vasopressors (89.2 % vs. 64.0 %, p = 0.006) and in those on RRT (95.8 % vs. 65.2 %, p = 0.006) at the time of CAPA diagnosis.

After the LASSO selection, nine variables were included in the multivariate Cox regression model (Table 4). In the multivariable model, an age ≥65 years (HR: 2.05, 95 % CI: 1.37–3.07), vasopressor need at CAPA diagnosis (HR: 1.80, 95 % CI: 1.17–2.76), and receiving RRT at CAPA diagnosis (HR: 2.27, 95 % CI: 1.35–3.82) were significant predictors for ICU mortality in patients with CAPA.

The decision tree split patients according to key predictors, including age, corticosteroid treatment for COVID-19, vasopressor need, and RRT at CAPA diagnosis (Fig. 3). Patients aged <65 years who did not receive vasopressor therapy and did not require RRT had lower mortality (estimated rate: 0.47, observed in 35 % of patients). In contrast, patients with CAPA aged ≥65 years who received corticosteroid treatment for COVID-19 displayed higher mortality rates (estimated rate: 1.6, observed in 46 % of patients).

4. Discussion

We conducted an extensive international multicenter study focusing on the mortality rates among patients with CAPA. Our findings

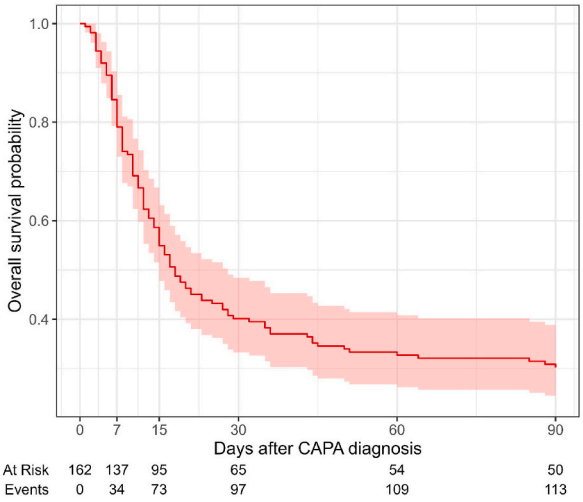

Fig. 2. Kaplan–Meier survival plot for intensive care unit mortality in patients with coronavirus disease (COVID-19)-associated pulmonary aspergillosis (CAPA).

Table 2
Comparison of demographic variables and treatments received for COVID-19 prior to CAPA diagnosis among the patients who survived and died.

	All, n = 162	Mortality		P*
		No, n = 49	Yes, n = 113	
Age				<0.001
<65 years	81 (50)	37 (45.7)	44 (54.3)	
≥65 years	81 (50)	12 (14.8)	69 (85.2)	
Sex				0.216
Male	106 (65.4)	36 (34.0)	70 (66.0)	
Female	56 (34.6)	13 (23.2)	43 (76.8)	
Comorbidities				0.507
No	19 (11.7)	4 (21.1)	15 (78.9)	
Yes	143 (88.3)	45 (31.5)	98 (68.5)	
Diabetes mellitus				0.514
No	78 (48.1)	26 (33.3)	52 (66.7)	
Yes	84 (51.9)	23 (27.4)	61 (72.6)	
Hypertension				0.008
No	110 (67.9)	41 (37.3)	69 (62.7)	
Yes	52 (32.1)	8 (15.4)	44 (84.6)	
Obesity				>0.999
No	140 (86.4)	42 (30.0)	98 (70.0)	
Yes	22 (13.6)	7 (31.8)	15 (68.2)	
Chronic obstructive pulmonary diseases				0.939
No	140 (86.4)	43 (30.7)	97 (69.3)	
Yes	22 (13.6)	6 (27.3)	16 (72.7)	
Malignancy				0.046
No	143 (88.3)	39 (27.3)	104 (72.7)	
Yes	19 (11.7)	10 (52.6)	9 (47.4)	
Chronic renal failure				0.109
No	144 (88.9)	47 (32.6)	97 (67.4)	
Yes	18 (11.1)	2 (11.1)	16 (88.9)	
Chronic heart diseases				>0.999
No	145 (89.5)	44 (30.3)	101 (69.7)	
Yes	17 (10.5)	5 (29.4)	12 (70.6)	
Hematopoietic stem cell or solid organ transplantation				0.324
No	157 (96.9)	49 (31.2)	108 (68.8)	
Yes	5 (3.09)	0 (0.00)	5 (100)	
Immunosuppressive therapy prior to COVID-19ɣ				0.329
No	137 (84.6)	44 (32.1)	93 (67.9)	
Yes	25 (15.4)	5 (20.0)	20 (80.0)	
Antiviral therapy for COVID-19				0.303
No	40 (24.7)	9 (22.5)	31 (77.5)	
Yes	122 (75.3)	40 (32.8)	82 (67.2)	
Corticosteroid treatment for COVID-19				0.068
No	10 (6.17)	6 (60.0)	4 (40.0)	
Yes	152 (93.8)	43 (28.3)	109 (71.7)	
Monoclonal antibody drug use for COVID-19				0.074
No	85 (52.5)	20 (23.5)	65 (76.5)	
Yes	77 (47.5)	29 (37.7)	48 (62.3)	
Broad-spectrum antimicrobial use prior to CAPA diagnosis				0.028
No	34 (21.0)	16 (47.1)	18 (52.9)	
Yes	128 (79.0)	33 (25.8)	95 (74.2)	
Invasive mechanical ventilation prior to CAPA diagnosis				0.609
No	34 (21.0)	12 (35.3)	22 (64.7)	
Yes	128 (79.0)	37 (28.9)	91 (71.1)	

CAPA, COVID-19-associated pulmonary aspergillosis; COVID-19, coronavirus disease.
Categorical variables are presented as numbers (percentages).
*P-value, Pearson's chi-square test or Fisher's exact test.
ɣUsing immunosuppressive medication or long-term steroids (prednisolone ≥20 mg/day for ≥4 weeks) in the 3 months prior to COVID-19.

were alarming: more than two-thirds of patients succumbed to the disease. Among the factors contributing to poor outcomes, older age was found to be a significant predictor of increased mortality, emphasizing the vulnerability of older individuals to severe consequences. Notably, the impact of corticosteroid use on mortality in patients aged >65 years was significant. Additionally, the use of vasopressors—which are commonly used to stabilize blood pressure—and the need for RRT in severe kidney dysfunction were linked to higher mortality rates, as expected. Our comprehensive study underscores the alarming mortality rates, particularly among older patients treated with corticosteroids.

Certain conditions weaken the immune system and increase the risk of IPA development. These include prolonged neutropenia, specific transplants (HSCT or SOT), inherited or acquired immune deficiencies, and the use of medications that suppress the immune system, such as steroids, monoclonal antibodies, or new cancer therapies [16]. A well-documented single-center cohort study

Table 3
Comparison of radiologic involvement and clinical variables at the time of CAPA diagnosis between the patients who survived and died.

	All, n = 162	Mortality		p
		No, n = 49	Yes, n = 113	
Site of aspergillosis involvement				0.022[a]
Only pulmonary	138 (85.2)	47 (34.1)	91 (65.9)	
Tracheobronchitis with pulmonary involvement	24 (14.8)	2 (8.33)	22 (91.7)	
SOFA score, median (25th–75th)	9.00 (5.00–11.0)	7.00 (4.50–10.0)	10.0 (6.00–11.0)	0.012[b]
Invasive Mechanical Ventilation at CAPA diagnosis				0.177[a]
No	40 (24.7)	16 (40.0)	24 (60.0)	
Yes	122 (75.3)	33 (27.0)	89 (73.0)	
Vasopressor need at CAPA diagnosis				0.006[a]
No	125 (77.2)	45 (36.0)	80 (64.0)	
Yes	37 (22.8)	4 (10.8)	33 (89.2)	
Renal replacement therapy at CAPA diagnosis				0.006[a]
No	138 (85.2)	48 (34.8)	90 (65.2)	
Yes	24 (14.8)	1 (4.2)	23 (95.8)	

CAPA, coronavirus disease (COVID-19)-associated pulmonary aspergillosis; SOFA, Sequential Organ Failure Assessment.
Categorical variables are presented as numbers (percentages).
[a] Pearson's Chi-squared test or Fisher's exact test.
[b] Mann–Whitney *U* test.

Table 4
Univariable and multivariable Cox proportional hazard models with LASSO-selected variables for mortality in patients with CAPA.

	Univariable		Multivariable	
	HR (95 % CI)	p	HR (95 % CI)	p
Age (≥65 years)	2.27 (1.55–3.33)	<0.001	2.05 (1.37–3.07)	<0.001
Diabetes mellitus	1.31 (0.91–1.90)	0.151	1.42 (0.95–2.13)	0.086
Hypertension	1.65 (1.13–2.42)	0.009	1.17 (0.79–1.75)	0.436
Chronic renal failure	1.66 (0.97–2.82)	0.063	1.22 (0.67–2.22)	0.516
Corticosteroid treatment for COVID-19	2.58 (0.95–7.01)	0.063	2.79 (0.99–7.88)	0.053
Broad-spectrum antimicrobial use prior to CAPA	1.97 (1.19–3.26)	0.009	1.52 (0.90–2.58)	0.117
Tracheobronchitis with pulmonary involvement	2.20 (1.37–3.53)	0.001	1.62 (0.99–2.64)	0.054
Vasopressor need at CAPA diagnosis	2.38 (1.58–3.58)	<0.001	1.80 (1.17–2.76)	0.008
Renal replacement therapy at CAPA diagnosis	2.38 (1.50–3.78)	0.001	2.27 (1.35–3.82)	0.002

CAPA, COVID-19-associated pulmonary aspergillosis; CI, confidence interval; COVID-19, coronavirus disease; HR, hazard ratio.

identified EORTC/MSGERC host factors in 45 % of patients with CAPA, showing a strong association between these factors and CAPA development [17]. When multiple multicenter studies on this topic were examined, slight variations were observed. In the first study, 27 % of patients with CAPA were found to have malignancies, SOTs, and chronic steroid treatment [18]. The second study observed the EORTC/MSGERC criteria in 13 % of the cohort [12]. However, our study revealed that only 18.5 % of the patients had a history of immunosuppressive therapy or transplantation. Multicenter studies, including our own, are believed to yield compatible results that closely resemble the real-world data. The emergence of IPA in cases lacking classical risk factors seems to result from damage to the physical barriers of the respiratory tract and a weakened immune response to fungal infection, including SARS-CoV-2 [19]. Consequently, severe COVID-19 is now acknowledged as a risk factor for IPA development.

Despite notable advancements, numerous challenges remain in the diagnosis of CAPA. This difficulty stems from the complexity of distinguishing the IPA findings on chest CT scans, as they may be obscured by the intricate patterns commonly associated with COVID-19 [7,20]. Furthermore, bronchoscopy—a valuable diagnostic procedure—is performed less frequently owing to safety concerns in certain circumstances or contexts. Earlier guidelines mainly advocated the use of bronchoscopic lavage and tissue biopsy for diagnosing IPA [3,21]. However, the ECMM/ISHAM consensus criteria now allow for the use of sputum or nonbronchoscopic lavage to diagnose CAPA [4]. This makes it difficult to distinguish between colonization and infection. There were cavitary lesions on thorax CT scans in half of our patients, paralleling the findings reported before [22].

Our investigation revealed that respiratory tract samples from a substantial majority of patients (60.9 %) exhibited growth of *Aspergillus* spp., consistent with the variable rates documented in the literature, ranging from 12.5 to 100 % [23]. Furthermore, bronchoscopic lavage GM and serum beta-D-glucan were tested in a subgroup of patients in this study, with positivity rates of 93.6 % and 37.5 %, respectively. Notably, Pavone et al. [24] conducted a study comparing the results of GM in endotracheal aspirate samples and serum beta-D-glucan and found similar outcomes: relying solely on imaging findings is inadequate to distinguish CAPA. The sensitivity of serum biomarkers is limited, and the presence of *Aspergillus* in the upper respiratory tract samples does not necessarily rule out colonization [25]. In conclusion, the most suitable diagnostic approach for CAPA appears to involve a combination of detecting *Aspergillus* in bronchoscopic lavage cultures and assessing GM positivity in bronchoscopic lavages.

The incidence of CAPA in the ICU is reported to range from 6.4 to 18.4 %, with high mortality rates ranging from 43 to 71 % as

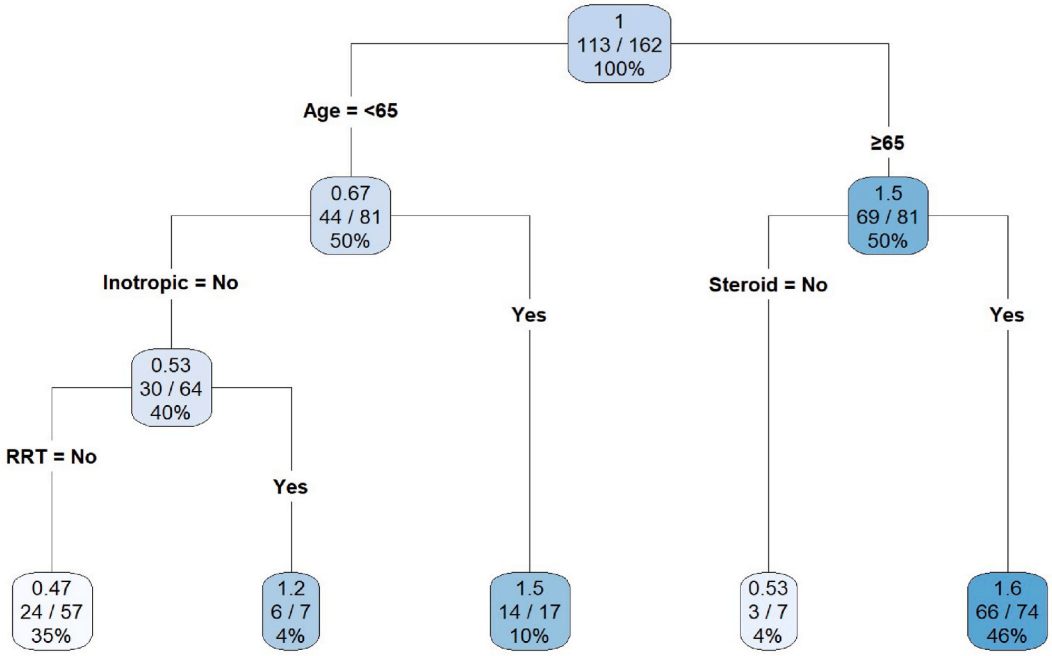

Fig. 3. Cox model decision tree analysis for intensive care unit mortality in coronavirus disease (COVID-19)-associated pulmonary aspergillosis. RRT, renal replacement therapy.

reported in the literature. IPA is also an independent factor that increases mortality in patients with COVID-19 [10,12,13,26–28]. Our findings revealed a mortality rate of 69.7 %, consistent with previous reports. When the factors affecting mortality before ICU admission were analyzed, we found that advanced age and corticosteroid use were associated with mortality in elderly patients. Advanced age, a factor widely recognized to increase mortality in patients with COVID-19 [1,29,30], was similarly linked to higher mortality in patients with IPA without immunocompromised host factors [31]. Nevertheless, the existing literature lacks sufficient data to precisely determine the effect of age on mortality in patients with CAPA. Both IPA and COVID-19, when considered separately, are believed to exhibit increased mortality rates with age. In contrast, corticosteroids—which are known for their positive effect on the severity of COVID-19 symptoms and mortality [32]—were associated with increased mortality in older patients with CAPA in our study. A study by Hashim et al. [13] on factors affecting mortality in patients with CAPA also demonstrated higher mortality rates among patients with CAPA receiving pulse steroids; a significantly increased risk of developing CAPA was observed in patients receiving steroids. Although corticosteroids have been demonstrated to reduce mortality in patients with COVID-19, they appear to increase the development of CAPA and CAPA-related mortality in selected patients [13,27,32,33]. Therefore, when considering the use of corticosteroids in COVID-19, it is imperative to carefully consider individual patient characteristics, such as age, and weigh the potential risks and benefits. Additional research is warranted to determine the optimal approach for balancing immunosuppression and infection risk in these patients, including the timing of corticosteroid therapy based on patient characteristics.

During the follow-up period in the ICU in our study, the administration of vasopressors and RRT was associated with mortality in patients with CAPA. These factors were found to be independent variables in the current study; this aligns with previous research [30], indicating a correlation between mortality and the use of vasopressors or kidney dysfunction in patients with COVID-19. These findings are believed to serve as indicators of septic shock and multiorgan failure, both of which are well-known factors that significantly contribute to increased mortality rates [34]. This was likely a result of severe respiratory failure associated with COVID-19, leading to the failure of multiple organs.

Our study has several limitations. First, this was a retrospective study lacking control groups that could help distinguish the impact of COVID-19 and *Aspergillus* infections on mortality. Second, the potential influence of other bacterial or fungal coinfections on prognosis may not have been adequately accounted for in our analysis. Third, differences in ICU protocols, diagnostic methods, and treatment regimens across centers could lead to variability in clinical outcomes. Fourth, bias may arise in the selection of patients and data quality due to the multiple participating centers. Finally, the specific causes of death were not determined.

4.1. Advances in knowledge

This study represents one of the most extensive and comprehensive international case series of CAPA reported to date and is the largest study to examine the predictors of mortality in this population. The inclusion of data from multiple centers across 15 countries enhances the generalizability of our findings, making them applicable to a broader range of clinical settings globally. The study findings have strong implications, as it was found that advanced age and the need for renal replacement therapy or vasopressor support

were potential factors associated with increased mortality in patients with CAPA. Additionally, elderly patients with CAPA who receive corticosteroids are at a significantly higher risk of mortality, particularly if they experience multiorgan failure.

4.2. Application to patient care

For people aged >65 years with a high risk of CAPA-related mortality, steroid use should be approached with caution by carefully weighing the risks and benefits. Lower doses and shorter treatment durations may be preferable if steroids are necessary. Additionally, close follow-up with intermittent bronchoscopic lavage for fungal culture and GM screening may help monitor and manage CAPA development in high-risk patients in the ICU. Our study also suggests that antifungal prophylaxis could help prevent IPA in patients with COVID-19 at a high risk of mortality. Further research is needed to confirm the benefits and necessity of antifungal prophylaxis in this population.

5. Conclusion

The incidence of aspergillosis is known to significantly increase due to lung damage caused by COVID-19, as well as due to the immunosuppressive effects of medications used for COVID-19 treatment. Our study identified advanced age and the need for RRT or vasopressor support as potential factors associated with increased mortality in patients with CAPA. Moreover, the notable increase in CAPA mortality with corticosteroid use in older patients is an impressive finding. These results should be considered when formulating CAPA diagnosis and treatment strategies, particularly for patients with a higher risk of mortality. Additionally, considering the high mortality associated with CAPA, IPA is frequently associated with severe COVID-19.

Ethical statement

This study was conducted in accordance with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of Istanbul Medipol University (number and date of ethical approval: E−10840098-772.02-1631 and March 05, 2022, respectively).

Disclosure statement

The authors have no competing interests to declare.

Data availability statement

Data will be made available on request.

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Informed consent statement

Patient consent was waived since the study was conducted retrospectively and relied on hospital registry data. All information was handled anonymously.

CRediT authorship contribution statement

Meyha Sahin: Writing – original draft, Data curation, Conceptualization. **Mesut Yilmaz:** Writing – review & editing, Supervision. **Ali Mert:** Writing – review & editing, Supervision. **Ahmet Naci Emecen:** Formal analysis. **Muna A. Rahman S. Al Maslamani:** Data curation. **Samar Mahmoud A. Hashim:** Data curation. **Ajithkumar Valooparambil Ittaman:** Data curation. **Jamal Wadi Al Ramahi:** Data curation. **Balint Gergely Szabo:** Data curation. **Deborah Konopnicki:** Data curation. **Dilsah Baskol Elik:** Data curation. **Botond Lakatos:** Data curation. **Oguz Resat Sipahi:** Supervision, Data curation. **Reham Khedr:** Data curation. **Sabah Jalal:** Data curation. **Natalia Pshenichnaya:** Data curation. **Dumitru Irina Magdalena:** Data curation. **Amani El-Kholy:** Data curation. **Ejaz Ahmed Khan:** Data curation. **Sevil Alkan:** Data curation. **Atousa Hakamifard:** Data curation. **Gulden Sincan:** Data curation. **Aliye Esmaoglu:** Data curation. **Mateja Jankovic Makek:** Data curation. **Esra Gurbuz:** Data curation. **Anna Liskova:** Data curation. **Ayse Albayrak:** Data curation. **Roman Stebel:** Data curation. **Tulay Unver Ulusoy:** Data curation. **Rezaul Karim Ripon:** Data curation. **Ruxandra Moroti:** Data curation. **Cosmin Dascalu:** Data curation. **Naveed Rashid:** Data curation. **Andrea Cortegiani:** Supervision, Data curation. **Zeynep Bahadir:** Data curation. **Hakan Erdem:** Writing – review & editing, Supervision, Methodology, Conceptualization.

Declaration of competing interest

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

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