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Risk Factors for Invasive Pulmonary Aspergillosis in Critically Ill Patients With Coronavirus Disease 2019-Induced Acute Respiratory Distress Syndrome

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Abstract: Severe coronavirus disease 2019 pneumonia can lead to acute respiratory distress syndrome. Recently, several publications reported on coronavirus disease 2019-associated pulmonary aspergillosis. However, risk factors remain unclear. We retrospectively collected all the cases of coronavirus disease 2019 acute respiratory distress syndrome patients ($n = 46$) admitted to our 34-bed ICU between March 24, 2020, and May 25, 2020, and identified six patients that met the diagnosis of invasive pulmonary aspergillosis according to previously established definitions. This population exhibited higher severity scores at admission and less hospital discharge compared with noninvasive pulmonary aspergillosis patients. Chronic obstructive pulmonary disease, malnutrition, and systemic corticosteroid use were identified as risk factors for invasive pulmonary aspergillosis in coronavirus disease 2019-induced acute respiratory distress syndrome patients. Coronavirus disease 2019-associated pulmonary aspergillosis may be a serious concern regarding corticosteroids use to control the inflammatory response of coronavirus disease 2019-induced acute respiratory distress syndrome.

Key Words: acute respiratory distress syndrome; aspergillus; coronavirus disease 2019; coronavirus; invasive pulmonary aspergillosis; systemic corticosteroids

Several authors have recently pointed out an abnormally high prevalence of invasive pulmonary aspergillosis (IPA) among the critically ill patients admitted for severe coronavirus disease 2019 (COVID-19) pneumonia in the ICU, especially those who

had developed an acute respiratory distress syndrome (ARDS) (1–3). To complete these first observations of COVID-19-associated pulmonary aspergillosis (CAPA), we investigated the prognosis and the associated risk factors of this opportunistic superinfection by *Aspergillus* species in our critically ill COVID-19 population. All the cases of COVID-19-induced ARDS patients admitted to our 34-bed ICU between March 24, 2020, and May 25, 2020 were retrospectively collected. All of them met the Berlin definition of ARDS and the diagnostic criteria for COVID-19 pneumonia (4). For the diagnosis of IPA, we considered the European Organization for Research and Treatment of Cancer Mycoses Study Group (EORTC-MSG), Aspergillosis in ICU (Asp-ICU), and modified Asp-ICU criteria simultaneously (5, 6). This retrospective observational single-center study was declared to the Commission Nationale de l'Informatique et des Libertés, the national commission of computer science and liberty. As the data were collected in an anonymized protected electronic file, the ethical review was waived. Data were expressed as median and interquartile range (25–75%) for continuous variables. Proportions were used as descriptive statistics for categorical variables. Comparisons of values between the groups were performed using a two-tailed Mann-Whitney U test. Analyses of discrete data were performed using Fisher exact test. p value of less than 0.05 was considered statistically significant. All reported p values were two-sided.

We included 46 patients with COVID-19 ARDS. Among them, six patients (13%) met the diagnostic criteria for IPA. The main characteristics of these patients are shown in **Table 1**.

The six IPA patients had a clinical picture and imaging compatible with the diagnosis of IPA. Five of them had a putative IPA (three according to the Asp-ICU algorithm and two according to Schauwvlieghe's modified Asp-ICU algorithm), and one patient had a possible IPA according to EORTC-MSG criteria (Table 1). An underlying immunodeficiency caused by immunosuppressive drugs—including rituximab, cyclophosphamide, and steroids—was observed in 2 of the IPA patients (33%). The first one had undergone solid organs transplantation, whereas the second one was treated for an myeloperoxidase-antineutrophil cytoplasmic antibodies-associated vasculitis. Aspergillosis mycological culture was positive in four

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TABLE 1. Main Characteristics of the Coronavirus Disease 2019 Acute Respiratory Distress Syndrome Patients With Documented Coronavirus Disease 2019-Associated Pulmonary Aspergillosis

Patient	1	2	3	4	5	6
Age (yr), gender	54, male	68, male	70, male	76, male	63, male	68, male
Medical history	AF, COPD, HT, OSAS, pulmonary HT, transient ischemic attack, congenital heart disease, and end-stage renal disease	Myeloperoxidase-antineutrophil cytoplasm antibodies associated vasculitis, chronic kidney disease, and nephrectomy	Junctional tachycardia, bipolar disorder, and HT	COPD, type 2 diabetes, hypercholesterolemia, hypothyroidism, and HT	AF, obesity, OSAS, and gastric ulcer	Atherosclerosis, AF, sarcopenia, and COPD
Immunosuppression	Heart and kidney transplantation	Immunosuppressive drugs for vasculitis	No	No	No	No
Admission Pao ₂ /Fio ₂ ratio (Berlin definition of ARDS)	218 (mild)	120 (moderate)	76 (severe)	48 (severe)	78 (severe)	128 (moderate)
Worst Sepsis-Related Organ Failure Assessment score	18	17	11	12	18	16
Steroids	Prednisone 10 mg/d (prior to admission)	Prednisone 5 mg/d (prior to admission)	Dexamethasone 20 mg/d (ARDS treatment)	Nasal mometasone furoate (prior to admission) and dexamethasone 20 mg/d (ARDS treatment)	No	Dexamethasone 20 mg/d (ARDS treatment)
Fungal culture	BAL: <i>Aspergillus fumigatus</i>	TA: <i>A. fumigatus</i>	–	–	BAL: <i>A. fumigatus</i>	TA: <i>A. fumigatus</i>
Bronchoalveolar lavage fluid galactomannan > 1	Positive	Not performed	Positive	Not performed	Not performed	Negative
Polymerase chain reaction <i>Aspergillus</i>	Not performed	TA: <i>A. fumigatus</i>	Not performed	Not performed	Not performed	Not performed
Invasive pulmonary aspergillosis definition	Asp-ICU algorithm: putative	Asp-ICU algorithm: putative	modified Asp-ICU algorithm: putative	European Organization for Research and Treatment of Cancer Mycoses Study Group possible	modified Asp-ICU algorithm: putative	Asp-ICU algorithm: putative
Delay after ICU admission (d)	6	14	32	9	3	6
Treatment	Lip. Ampho. B	Lip. Ampho. B	Caspofugin	–	Voriconazole and isavuconazole	Voriconazole
Outcome	Alive	Died	Died	Died	Died	Alive
Hospital stay if alive	> 60 d	–	–	–	–	> 60 d

AF = atrial fibrillation, ARDS = acute respiratory distress syndrome, Asp-ICU = diagnosis algorithm for aspergillosis in ICU, BAL = bronchoalveolar lavage, COPD = chronic obstructive pulmonary disease, HT = hypertension, Lip. Ampho. B = liposomal amphotericin B, OSAS = obstructive sleep apnea syndrome, TA = tracheal aspirates.

TABLE 2. Comparison of Coronavirus Disease 2019 Acute Respiratory Distress Syndrome Patients With and Without Invasive Pulmonary Aspergillosis

Variables	IPA (n = 6)	Non-IPA (n = 40)	p
Demographic characteristics			
Age (yr)	68 (60.7–71.5)	66 (55.5–70)	0.5
Gender male, n (%)	6 (100)	29 (72.5)	0.31
Comorbidities			
Obesity (body mass index > 30 kg/m ²), n (%)	3 (50)	30 (75)	0.33
Diabetes, n (%)	2 (33.3)	17 (42.5)	1
Chronic obstructive pulmonary disease, n (%)	3 (7.5)	3 (50)	0.022
Cancer, n (%)	0 (0)	6 (15)	0.59
Immunosuppression except steroids, n (%)	2 (33.3)	3 (7.5)	0.12
Frailty score	3 (3–4.2)	2 (2–3)	0.039
Charlson comorbidity index	2 (2–2.7)	1 (1–2)	0.07
Severity scores at ICU admission			
Sepsis-Related Organ Failure Assessment score	10.5 (6.2–12.2)	5.5 (4–7)	0.047
Simplified Acute Physiology Score II	67.5 (60–74)	38 (28–58.7)	0.002
Laboratory data at ICU admission			
Albumin (g/L)	19.5 (17–22.7)	26.5 (23–31.7)	0.001
C-reactive protein (mg/L)	289.5 (143.7–374)	171 (115–230.7)	0.064
Leukocytes (G/L)	9.3 (7.1–18.1)	8.6 (5.9–10.9)	0.25
Creatinine (μmol/L)	85.5 (50–141)	70 (56.2–100)	0.81
Pao ₂ /Fio ₂ (mm Hg)	76.9 (1.1–150.4)	114.1 (97.4–143.5)	0.18
Outcome			
ICU death, n (%)	4 (66.7)	10 (25)	0.06
Hospital discharge before 60 d, n (%)	0 (0)	30 (75)	0.001
Systemic corticosteroids use, n (%)	5 (83.3)	4 (10)	0.001

IPA = invasive pulmonary aspergillosis.

Boldface entries represent either the subparts (e.g., “Demographic characteristics”, “Comorbidities”) or highlight the significant p values (p < 0.05).

patients. *Aspergillus fumigatus* was the only species found. Tests for antifungal treatment susceptibility were performed in patients 2, 5, and 6 and showed sensitivity for azole agents and Amphotericin B. Bronchioalveolar lavage fluid galactomannan index was greater than 1 in two patients. Patient 4 in Table 1 had host factors (steroids treatment) and clinical features of fulminant IPA. The rapid deterioration in this patient’s respiratory condition is illustrated in **Supplemental Figure 1** (<http://links.lww.com/CCX/A396>), which shows left lung’s excavation in less than 3 days. Unfortunately, the patient died before any mycological identification test could be done, and no antifungal treatment was administered before the patient’s death. Despite optimal antifungal therapy by voriconazole in five patients, only two patients survived and none were weaned off from the ventilatory support and discharged from ICU after 60 days of hospitalization. The comparisons of the six IPA patients to the 40 non-IPA patients are detailed in **Table 2**. The IPA group included frailer individuals, and exhibited

higher severity scores at ICU admission and less hospital discharge within 60 days than the non-IPA patients. Chronic obstructive pulmonary disease (COPD) was more present, and albumin level was significantly lower in the IPA group than that in the non-IPA patients at admission. Systemic corticosteroids were also more frequently used in IPA patients (Table 2). Five out of the six IPA patients received systemic corticosteroids: before the admission in two patients and as an adjunctive treatment for ARDS in three patients.

The main findings of the present study can be summarized as follows: 1) IPA is not only associated with COVID-19-induced ARDS but also impacts patients’ outcome and 2) the risk factors of COVID-19-associated IPA include COPD as comorbidity, low albumin level at ICU admission, high frailty and severity scores, and the use of steroids.

Recently, COPD has been identified as a risk factor for CAPA by Wang et al (2). Before the COVID-19 pandemic, COPD was already

considered as a classic risk factor for IPA (7). This may partly be explained by the widespread use of steroids in COPD exacerbations. Considering non-COVID-19 ICU patients, several risk factors of IPA had been identified in nonimmunocompromised hosts, including malnutrition and diabetes. In the study by Ghanaat and Tayek (8), 65% of IPA patients had experienced weight loss before admission. In our COVID-19 critically ill population, hypoalbuminemia clearly reflected malnutrition. A higher prevalence of systemic corticosteroid use has been reported by van Arkel et al (1). Similarly, Wang et al (2) and Alanio et al (3) observed that six CAPA patients out of eight and six CAPA patients out of nine received steroids to treat COVID-19 pneumonia. In our study, systemic corticosteroid use appears to be statistically associated with CAPA. Consistent with this observation, corticosteroids have been considered in previous studies as the most common risk factor for IPA in immunocompetent hosts (9). More recently, a preliminary report of the large RECOVERY randomized clinical trial supported the use of dexamethasone by demonstrating a lower 28-day mortality in the COVID-19 population needing oxygen or mechanical ventilatory support and treated with small doses of corticosteroids (10). We thus assume that CAPA cases might increase further. Given the single-center retrospective observational study design, we must acknowledge that our results should be confirmed in a large population allowing a multivariate analysis of the data. However, our findings might question the use of steroids in vulnerable individuals with COVID-19 pneumonia at high risk of IPA and emphasize the need for aspergillosis screening in this population.

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