Original Research

# Potential links between COVID-19-associated pulmonary aspergillosis and bronchiectasis as detected by high resolution computed tomography

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## 1. Abstract

**Purpose**: The aim of this observational study was to highlight high resolution CT scan characteristics of COVID-19-associated pulmonary aspergillosis (CAPA) with a focus on the detection of de-novo appeared or evolved bronchiectasis. **Methods**: From March 2020 to May 2021, we enrolled 350 consecutive mechanically ventilated ICU patients with COVID-19. Patients with CAPA and at least one chest CT scan performed within 15 days from the diagnosis were included. Two radiologists were asked to identify typical and atypical signs of COVID-19 pneumonia. Bronchiectasis locations were described and a modified Reiff score was calculated, as severity score. A total of 19 CAPA patients (median age 71.0, Interquartile range (IQR) 62.5–75.0; male 16, 84.2%) were included. **Results**: According to the 2020 ECMM/ISHAM criteria, 18 patients had probable CAPA and one had proven CAPA. The median time between hospital admission and CT scan was 21 days (IQR 14.5–25.0). The incidence of bronchiectasis in the study population was 57.9% (n = 11). Tubular bronchiectasis was detected in 10 patients and were scored as follows: three patients had a score of 1, three patients had a score of score 2, one patient had a score of 5 and four patients had a score of 6. Eight patients had a previous CT scan (performed at hospital admission), among them: 5 patients developed de-novo bronchiectasis, while 2 patients demonstrated a volumetric increase of bronchiectasis. At the 6-months follow-up, the mortality rate for patients with CAPA was >60%. **Conclusion**: the radiologic detection of de-novo appearance or volumetric increase of bronchiectasis in COVID-19 should lead clinicians to search for fungal superinfections.

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## 2. Introduction

Immunodeficiency and tissue damage are the common basis of viral and fungal infections. When viruses cause tissue activation of immunity with severe clinical consequences, such as the SARS-CoV-2 leading to severe pneumonia, the possibility of a superinfection is not so rare [1]. The most common superimposed infection in a COVID-19 patient is usually bacterial, however mycoses may appear as a result of an immunity derangement and increase the mortality rates [2]. The COVID-19 pandemic has shed light on the emerging recognition of pulmonary aspergillosis superinfections among SARS-CoV-2 infected patients. Studies report that aspergillosis complicates 7–28% of COVID-19 cases [3] with a mortality rate of approximately 50% [4]. These data are not surprising since studies on intensive care unit (ICU) influenza patients reported that 19% of them were diagnosed with pulmonary aspergillosis after a median of 3 days after ICU admission (32% among immunocompromised and 14% among non-immunocompromised patients) [4, 5]. From a speculative point of view, apart from the virus-induced immunosuppression, COVID-19 patients are more prone to receive corticosteroids compared to influenza patients. Indeed the role of corticosteroids in influenza is controversial and not recommended by the guidelines [6], on the other hand, in COVID-19 hospitalized patients with pneumonia, robust evidence supports the use of prolonged low dose corticosteroids [7]. Similarly, although with weaker evidence, monoclonal antibodies against interleukins (especially IL-1 and IL-6) have been commonly used in COVID-19 patients and further contribute to immunosuppression.

Although approximately 43–80% of the cases of invasive aspergillosis have been observed in patients without a hematological malignancy [8], the diagnostic criteria are usually tailored on neutropenic patients and solid organ or stem cell transplant patients. This poses difficulties in the interpretation of diagnostic tests for aspergillosis. For example, serum galactomannan testing is significantly lower in non-neutropenic versus neutropenic patients [6, 9]. This has led to the classification of COVID-19-associated pulmonary aspergillosis (CAPA) as a new disease entity, and recently ad hoc consensus criteria and clinical guidance have been published [10].

Conventional radiological criteria for use in the suspicion of invasive pulmonary Aspergillosis in neutropenic patients have been already established and defined (e.g., solid nodules, halo signs, cavitation and air crescent signs) [11]. However, to date, there are no criteria for other groups of patients, due to the non-specific radiological findings.

Bronchiectasis have been associated with fungal or mycobacterial colonizations and their presence at baseline or their de-novo appearance or volumetric increase could potentially provide evidence concerning the risk of fungal superinfections.

The aim of this observational study was to highlight high resolution CT scan characteristics for CAPA in COVID-19 in order to early suspect the possibility of this co-infection in patients with severe SARS-CoV-2 infection, with a focus on bronchiectasis.

## 3. Methods

A retrospective observational study was conducted from March 2020 to May 2021 in Trieste University Hospital: 350 consecutive mechanically ventilated patients admitted to the ICU for severe acute respiratory failure due to COVID-19 were enrolled.

All the consecutive CAPA patients were reported and reviewed, focusing on clinico-radiological features of bronchiectasis.

Our study population consists of COVID-19 mechanically ventilated patients who met the following criteria:

(1) Age $\geq$18 years.

(2) CAPA diagnosis (possible, probable, proven) according to Koehler *et al*. [10].

(3) At least one chest CT scan performed within 15 days from the diagnosis of CAPA.

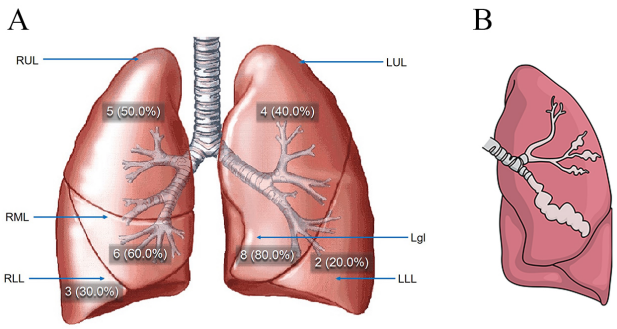


**Fig. 1. Anatomic distribution and type of bronchiectasis.** (A) The sum of percentages exceeds 100% since patients could have lesions in more than one lobe. Lgl, lingula; LLL, left lower lobe; LUL, left upper lobe; RML, right middle lobe; RLL, right lower lobe; RUL, right upper lobe. (B) The radiological severity of bronchiectasis was assessed applying a modified Reiff score, were the number of lobes involved is taken into consideration (6 lobes in total, considering the lingula as a separate lobe) and the degree of bronchial dilatation (tubular bronchiectasis = 1 point, varicose bronchiectasis = 2 points and cystic bronchiectasis = 3 points).

Any patients with a previous history of interstitial lung diseases were excluded.

The relevant demographic and clinical data were extracted from electronic medical records or charts and anonymously coded onto a standardized data collection form. Mortality was defined as death from any cause within six months from hospital admission.

Volumetric contrast enhanced CT images were acquired using a CT scan dedicated to COVID-19 patients (Revolution EVO GE Healthcare, Chalfont St Giles, United Kingdom) and all images were reconstructed with a slice thickness of 1 mm and lung sharp kernels. The imaging protocol established that all patients must have a volumetric CT scan, performed during single breath hold at full inspiration in a supine position. All CT images were evaluated by two senior radiologists with expertise in thoracic imaging. The CT images were analyzed at standard lung window settings (a window level of –600 HU and a window width of 1600 HU) and mediastinal window settings (a window level 400 HU and a window width 40 HU).

Although the readers reviewing CT images were made aware of the COVID-19 status of the patients, they were blinded to other clinical information. They were asked to identify typical (i.e., peripheral ground-glass opacities with or without airspace consolidations and crazy paving) and atypical (i.e., parenchymal nodules, halo signs, bronchiectasis and bronchiolectasis, bronchial wall thickening, cavitation, air crescent signs, tree-in-bud) parenchymal signs of COVID-19 pneumonia. Moreover, the presence of pneumomediastinum and pleural effusion was reported. These imaging findings were categorized as present or absent. When bronchiectasis were identified, their locations were described according to the pulmonary lobar subdivisions and radiological severity score was assigned using a modified Reiff score, ranging from 1 to 18 [12].

Moreover if a CT scan was performed at hospital admission, readers were asked to evaluate the presence or absence of bronchiectasis.

The continuous variables were described as medians and interquartile ranges (IQRs) and the nominal variables as numbers and percentages. Bivariate comparisons between subjects with or without bronchiectasis were performed via a Fisher's exact test or nonparametric Mann-Whitney's U test, as appropriate.

## 4. Results

A total of 19 consecutive patients (median age 71.0, IQR 62.5–75.0; male 16, 84.2%) met the inclusion criteria and were included in the dataset. The median SOFA score on ICU admission was 4.0 (IQR 4.0–6.5). All patients received steroid therapy prior to aspergillosis diagnosis. Five patients received anti IL-6 treatment consisting in tocilizumab, whilst none received IL-1 inhibitors.

All patients underwent bronchoscopy. The median duration of mechanical ventilation prior to the bronchoscopy was 11 days (IQR 3.0–16.5). In all patients but one *Aspergillus* was detected in bronchoalveolar lavage samples, by culture in seven cases, by PCR in seven cases, and by both tests in four cases. For those with available *Aspergillus* DNA, the higher median fungal load was 13,000 cp/mL (IQR 1300–22,500 cp/mL). BAL galactomannan was measured in 17 patients and was positive (index $\geq$1) in 10 cases (58.8%). Serum galactomannan was measured in 12 patients and was positive (index $\geq$0.5) in one case. According to the 2020 ECMM/ISHAM criteria, all patients had probable CAPA except for one who had proven CAPA. The main characteristics of CAPA patients with and without bronchiectasis are summarized in Table 1.

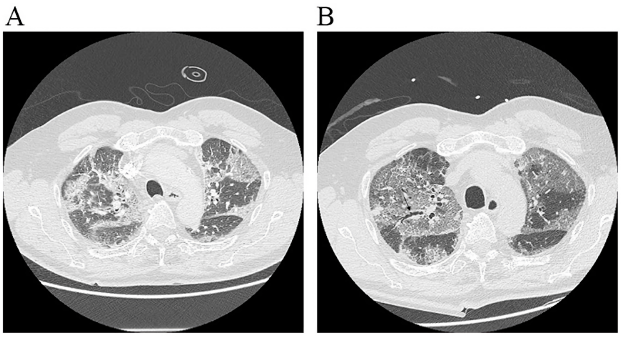


**Fig. 2. A 74-year-old male patient with a diagnosis of CAPA.** (A) The Axial High resolution CT image evidences bronchial wall thickening in the upper right lobe (white arrow). (B) An HRCT scan performed 15 days later evidenced the development of varicose bronchiectasis (black arrow) at the same level.

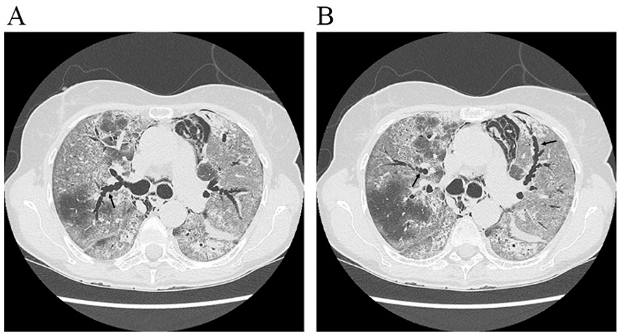


**Fig. 3. A 71-year-old male.** Tubular bronchiectasis were evidenced in 2 lobes while varicose bronchiectasis (black arrows) were evidenced in the right (A) and in the left (B) upper lobe; the CT scan was given a score of 6.

The median time between hospital admission and chest CT scan was 21 days (IQR 14.5–25.0). Diffuse ground glass opacities and airspace consolidations were identified in all patients. Moreover, crazy-paving areas were found in six subjects, pleural effusion in nine (seven bilateral, two unilateral), pneumomediastinum in two, cavitation within consolidation areas and diffuse parenchymal nodules in two other patients. No patients had air crescent signs, halo signs or bronchial wall thickening. Overall, the incidence of bronchiectasis in the study population was 57.9% (n = 11). Fig. 1 shows the anatomic distribution of the bronchiectasis. Tubular bronchiectasis was found in 10

**Table 1. Main characteristics of COVID-19-associated pulmonary aspergillosis patients with and without bronchiectasis.**

| Variable | Bronchiectasis | |
|---|---|---|
| | No (n = 8) | Yes (n = 11) |
| Age (years) median, IQR | 67.0; 61.5–73.0 | 72.0; 62.0–76.0 |
| Sex (male) n, % | *6 (75.0%)* | *10 (90.9%)* |
| H admission-HRCT (days) median, IQR | 19.0; 14.0–26.5 | 22.0; 14.0–24.0 |
| SOFA at ICU admission IQR | 4.5; 4.0–7.5 | 4.0; 4.0–6.0 |
| Active smoker (yes) n, % | *1 (12.5%)* | *2 (18.2%)* |
| COPD (yes) n, % | *4 (50.0%)* | *1 (9.1%)* |
| Obesity (yes) n, % | *4 (50.0%)* | *4 (36.4%)* |
| Diabetes (yes) n, % | *1 (12.5%)* | *2 (18.2%)* |
| Hypertension (yes) n, % | *6 (75.0%)* | *7 (63.6%)* |
| Chronic kidney failure (yes) n, % | *2 (25.0%)* | *0 (0.0%)* |
| Heart disease (yes) n, % | *2 (25.0%)* | *1 (9.1%)* |
| Tocilizumab (yes) n, % | *1 (12.5%)* | *4 (36.4%)* |
| Six-months mortality (n = 18) | *6 (85.7%)* | *6 (54.5%)* |

No between-group statistically significant difference.

COPD, Chronic Obstructive Pulmonary Disease; HRCT, High Resolution Computed Tomography; ICU, Intensive Care Unit; SOFA, Sequential Organ Failure Assessment.

Plan text: median; interquartile range. Italic text: number (percentage).

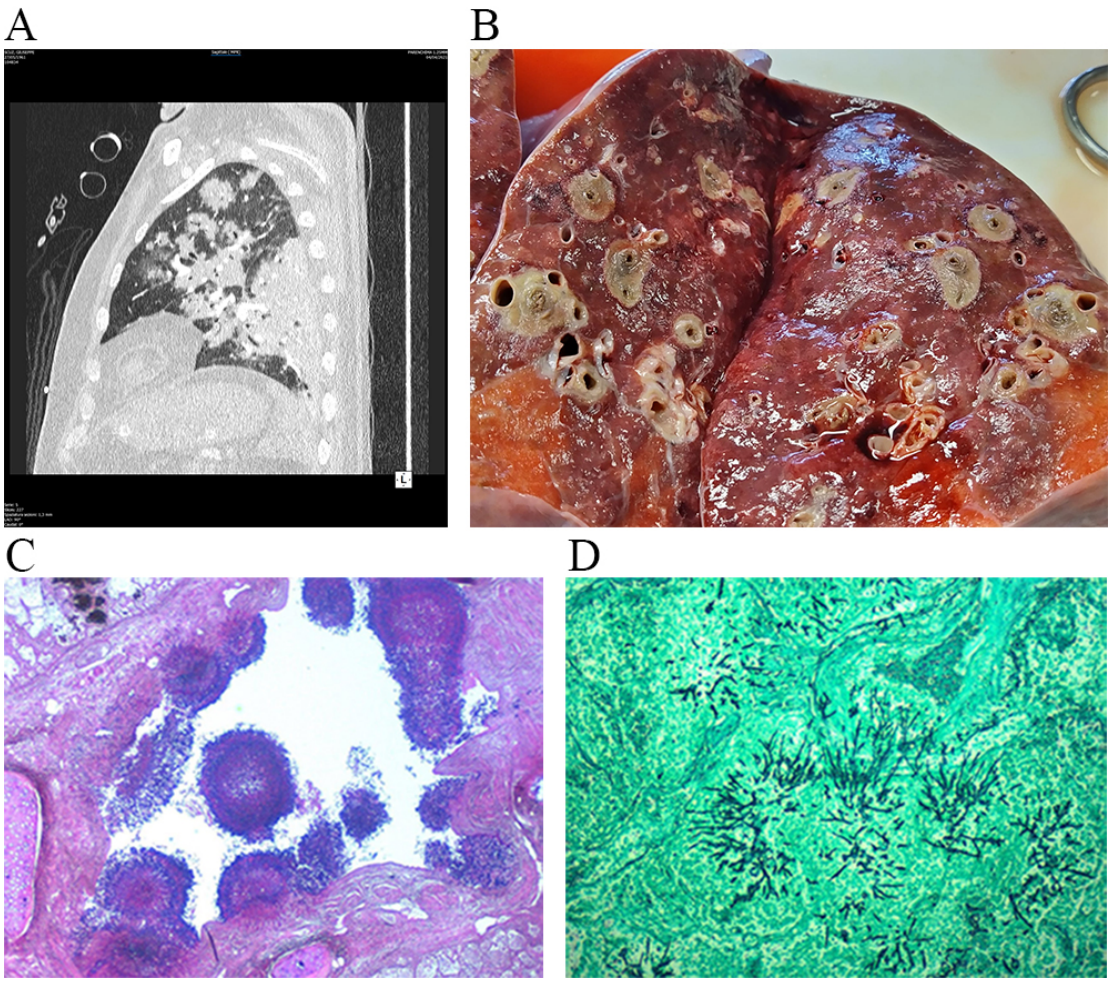


**Fig. 4. A 60-year-old male patient.** (A) Diffuse consolidations, more prominent in the left lower lobe. Diffuse lung nodules can clearly be observed on the High Resolution CT scan (sagittal plane). (B) peribronchial aspergillosis in a post-mortem COVID-19 lung. (C) endobronchial aspergillosis at Hematoxilyn & Eosin staining (2.5×). (D) Aspergillus hyphae identified by Grocott-Gomori stain (10×).

patients, 3/10 had associated varicose bronchiectasis, whilst 1 patient had varicose bronchiectasis alone (Figs. 2,3). The bronchiectasis score was 1 in 3 patients, 2 in 3 other patients, 5 in 1 patient and 6 in 4.

In 8 patients a CT scan was also performed at hospital admission. Among them, 5 patients developed de-novo bronchiectasis, while 2 patients demonstrated a volumetric increase of bronchiectasis on CT scan performed at the diagnosis of CAPA.

At the end of the study one patient was still in ICU. For the remaining 18 patients, the 6-months mortality rate was 54.5% (6 out of 11) among patients with bronchiectasis and 85.7% (6 out of 7) among those without bronchiectasis.

A comparison of CT images and post-mortem autoptic tissue is illustrated in Fig. 4.

## 5. Discussion

Only 1/9 of our patients had "classical" fungal imaging with cavitation and one with diffuse parenchymal nodules. Conversely, bronchiectasis was a common finding among our CAPA patients and was observed in more than half of cases (57.9%). The vast majority of the pulmonary bronchiectasis involvement was localized in the lingula (80%) and medial lobe (60%) and this distribution can be explained by the absence of collateral ventilation and their anatomical structure in these lobes, which makes it difficult to clear secretions [13].

Bronchiectasis are commonly accompanied by microbial colonizations [14] and *Aspergillus* is certainly a fungus with a great pathogenic potential. In patients with bronchiectasis fungal growth is enhanced by deteriorated mucociliary clearance, thick mucosity and the capability to escape the immune system response. Moreover, all our patients were administered selective digestive decontamination plus intravenous cefotaxime for 4 days as local ICU protocol and this may have contributed to the fungal overgrowth.

Although classical radiological criteria for the suspicious of invasive pulmonary Aspergillosis in neutropenic patients are well established and include "halo signs", cavitation and "air crescent signs", to date there are no criteria suitable for other group of patients, since radiological findings are not specific [15]. However, recently these criteria have been revised and wedge-shape lobar or segmental consolidation have been included in the radiological classification [16].

Regarding mortality, 54.5% (6/11) of patients with bronchiectasis died.

From a pathogenetic point of view, CAPA is more similar to an "extended endobronchial aspergillosis" than to invasive aspergillosis. What we identified in our personal experience is a progressive malacia of bronchus with an often mildly invasive involvement of the peribronchial tissue.

Patients with severe COVID-19 pneumonia in mechanical ventilation are at risk for co-infections. Since radiological findings of pulmonary infiltrates are non-specific and may overlap in patients with severe COVID-19 pneumonia, it remains challenging to make a radiological suspicion of CAPA.

Bearing this in mind, we believe that the identification of bronchiectasis could be used as a radiologic criterion to suspect CAPA, in fact *Aspergillus* is a well-known colonizer of bronchiectasis and can "switch into pathogenic mode" from there, or it may lead "de-novo"-appeared bronchiectasis or worsening of previous existing ones.

Our study has several limitations but the main one is that we cannot be certain of the pathogenic role of *Aspergillus* in all except one of our patients because we do not have the *in vitam* histology, but this is a common problem when caring for these patients. Anyhow, the remaining patients had a diagnosis of probable CAPA according to the 2020 ECMM/ISHAM criteria. Other limitations include the retrospective design of the study and the limited number of cases. Nothwithstanding these limitations, the thoracic CT scan of all our patients were accurately reviewed by two radiologists aware of the COVID-19 status of the patients but blinded to other clinical information.

When having to interpret the imaging of COVID-19 patients' lungs, it is very difficult to understand the quote of the pleuroparenchymal alterations attributable to SARS-CoV-2 and that attributable to a potential superinfection. Our data suggest that "de-novo" or worsening bronchiectasis in COVID-19 patients especially in the lingula and medial lobe may be warning signs for radiologists. The observation of bronchiectasis in the chest CT of a COVID-19 patient should prompt the clinician to take into account the hypothesis of a fungal superinfection and consequently prompt further diagnostic investigation along these lines.

## 6. Conclusions

Mortality of CAPA is quite high. Bronchiectasis are a common finding in our CAPA patients. While bronchiectasis can develop during different kind of infection, they are not typical radiological findings related to COVID-19 pneumonia. According to our data, a diagnosis of CAPA should be suspected especially in patients with severe COVID-19 who have, develop, or worsen bronchiectasis on CT scan. Further studies are ongoing to evaluate the prognostic role bronchiectasis play in the natural history of CAPA.

In conclusion severe COVID-19 patients with bronchiectasis should promptly require diagnostic tests to exclude fungal superinfections.

## 7. Author contributions

Conceptualization—EB, ERP, VZ, GS, FF, PM, MAC, RB, MP, MB, FS and SDB; writing—original draft preparation—EB, BR, SDB, VZ and GS; writing—review and editing—BR, BW, AB, RP and AGA; supervision—RL, UL, MAC and MC. All authors have read and agreed to the published version of the manuscript.

## 8. Ethics approval and consent to participate

Informed consent was obtained from all subjects involved in the study. The study was approved by the Local Ethical Committee (CEUR-2020-Os-148) and carried out in accordance with the Helsinki Declaration.

## 9. Acknowledgment

Not applicable.

## 10. Funding

This research received no external funding.

## 11. Conflict of interest

The authors declare no conflict of interest. BR is serving as one of the Editorial Board members of this journal. We declare that BR had no involvement in the peer review of this article and has no access to information regarding its peer review. Full responsibility for the editorial process for this article was delegated to GP.

## 12. References

[1] Giacobbe DR, Battaglini D, Enrile EM, Dentone C, Vena A, Robba C, *et al*. Incidence and Prognosis of Ventilator-Associated Pneumonia in Critically Ill Patients with COVID-19: A Multicenter Study. Journal of Clinical Medicine. 2021; 10: 555.

[2] Gagneux JP, Dannaoui E, Fekkar A, Luyt CE, Botterel F, De Prost N, *et al*. Fungal infections in mechanically ventilated patients with COVID-19 during the first wave: the French multicentre MYCOVID study. The Lancet Respiratory Medicine. 2021. (in press)

[3] Borman AM, Palmer MD, Fraser M, Patterson Z, Mann C, Oliver D, *et al*. COVID-19-Associated Invasive Aspergillosis: Data from the UK National Mycology Reference Laboratory. Journal of Clinical Microbiology. 2020; 59: e02136-20.

[4] Singh S, Verma N, Kanaujia R, Chakrabarti A, Rudramurthy SM. Mortality in critically ill patients with coronavirus disease 2019-associated pulmonary aspergillosis: a systematic review and meta-analysis. Mycoses. 2021; 64: 1015–1027.

[5] Schauwvlieghe AFAD, Rijnders BJA, Philips N, Verwijs R, Vanderbeke L, Van Tienen C, *et al*. Invasive aspergillosis in patients admitted to the intensive care unit with severe influenza: a retrospective cohort study. The Lancet. Respiratory Medicine. 2018; 6: 782–792.

[6] Uyeki TM, Bernstein HH, Bradley JS, Englund JA, File TM, Fry AM, *et al*. Clinical Practice Guidelines by the Infectious Diseases Society of America: 2018 Update on Diagnosis, Treatment, Chemoprophylaxis, and Institutional Outbreak Management of Seasonal Influenza. Clinical Infectious Diseases. 2019; 68: 895–902.

[7] Salton F, Confalonieri P, Meduri GU, Santus P, Harari S, Scala R, *et al*. Prolonged Low-Dose Methylprednisolone in Patients with Severe COVID-19 Pneumonia. Open Forum Infectious Diseases. 2020; 7: ofaa421.

[8] Ullmann AJ, Aguado JM, Arikan-Akdagli S, Denning DW, Groll AH, Lagrou K, *et al*. Diagnosis and management of Aspergillus diseases: executive summary of the 2017 ESCMID-ECMM-ERS guideline. Clinical Microbiology and Infection. 2018; 24: e1–e38.

[9] Teering S, Verreth A, Peeters A, Van Regenmortel N, De Laet I, Schoonheydt K, *et al*. Prognostic value of serum galactomannan in mixed ICU patients: a retrospective observational study. Anaesthesiology Intensive Therapy. 2014; 46: 145–154.

[10] Koehler P, Bassetti M, Chakrabarti A, Chen SCA, Colombo AL, Hoenigl M, *et al*. Defining and managing COVID-19-associated pulmonary aspergillosis: the 2020 ECMM/ISHAM consensus criteria for research and clinical guidance. The Lancet Infectious Diseases. 2021; 21: e149–e162.

[11] Stevens DA, Kan VL, Judson MA, Morrison VA, Dummer S, Denning DW, *et al*. Practice Guidelines for Diseases Caused by Aspergillus. Clinical Infectious Diseases. 2000; 30: 696–709.

[12] Chalmers JD, Goeminne P, Aliberti S, McDonnell MJ, Lonni S, Davidson J, *et al*. The Bronchiectasis Severity Index. an International Derivation and Validation Study. American Journal of Respiratory and Critical Care Medicine. 2014; 189: 576–585.

[13] Gudbjartsson T, Gudmundsson G. Middle Lobe Syndrome: a Review of Clinicopathological Features, Diagnosis and Treatment. Respiration. 2012; 84: 80–86.

[14] Máiz L, Nieto R, Cantón R, Gómez G de la Pedrosa E, Martinez-García MÁ. Fungi in Bronchiectasis: a Concise Review. International Journal of Molecular Sciences. 2018; 19: 142.

[15] Jenks JD, Nam HH, Hoenigl M. Invasive aspergillosis in critically ill patients: Review of definitions and diagnostic approaches. Mycoses. 2021; 64: 1002–1014.

[16] Donnelly JP, Chen SC, Kauffman CA, Steinbach WJ, Baddley JW, Verweij PE, *et al*. Revision and Update of the Consensus Definitions of Invasive Fungal Disease From the European Organization for Research and Treatment of Cancer and the Mycoses Study Group Education and Research Consortium. Clinical Infectious Diseases. 2020; 71: 1367–1376.

**Abbreviations:** CAPA, COVID-19 associated pulmonary Aspergillosis; HRCT, High Resolution CT; ICU, Intensive Care Unit; SOFA score, Sequential Organ Failure Assessment Score.

**Keywords:** COVID-19; Pulmonary aspergillosis; High resolution CT; Bronchiectasis; Intensive care unit; Acute respiratory distress syndrome; Pulmonary infection

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