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Invasive fungal infections in critically ill COVID-19 patients in a large tertiary university hospital in Israel

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ABSTRACT

An increasing number of studies have tried to determine the incidence of invasive fungal infections (IFIs) in COVID-19 patients. Challenges in the diagnosis of pulmonary aspergillosis in these patients have led to new definitions of COVID-19-associated pulmonary aspergillosis (CAPA). The aim of this study was to determine the incidence and outcomes of and risk factors for IFIs in critically-ill COVID-19 patients, using the new definitions, in a tertiary center in Israel.

Methods: A case-controlled study (from 1 September 2020 to 31 March 2021) in which data from COVID-19 critically-ill patients with a diagnosis of IFI were collected and compared to a control group without IFI.

Results: The incidence of IFI amongst 311 COVID-19 critically-ill patients was 6.1%. 3.5% had CAPA and 3.5% had candidemia. In-hospital mortality was higher amongst patients with IFI compared to those without IFI (89.4% vs 60%, $p < 0.03$). The most significant predictors of IFI were cardiovascular co-morbidity and carbapenem use.

Conclusions: The low incidence of CAPA in our group of COVID-19 critically-ill patients was consistent with recent reports, underscoring the importance of differentiating between true infection and colonization. Awareness and timely diagnosis of IFIs in COVID-19 critically-ill patients are imperative considering the associated high mortality.

1. Introduction

Since Corona virus disease 2019 (COVID-19) emerged in our lives in December 2019, approximately 250 million confirmed cases have been reported with over 5 million deaths worldwide [1].

The lung damage caused by the virus, often resulting in intensive care admission, may be associated with secondary infections shortly after disease onset [2]. Co-pathogens reported in COVID-19 patients are mainly bacteria causing lower respiratory tract infections [3], but fungal infections were also reported and associated with severe illness and death [4]. Several studies have reported the occurrence of COVID-19-associated invasive fungal infection (IFI), mostly pulmonary aspergillosis and candidemia, complicating the clinical course of these patients [5-7]. In several studies, a higher 30-day mortality was observed in critically ill patients with COVID-19 associated pulmonary aspergillosis (CAPA) than in patients without aspergillosis (44% vs 19%) [8,9]. Predisposing factors for CAPA include diffuse alveolar damage with severe inflammatory exudation, immunosuppression with decreased CD4+ and CD8+ T cells, mechanical ventilation and a prolonged hospital stay [10,11].

Early studies from China, have reported different rates of *Aspergillus* co-infection amongst patients with COVID-19. The estimated rates in these studies were as high as 20–33% in severely- and critically-ill patients, but they lacked standardization of diagnostic criteria [12,13]. Recent reports from France and Utah have tried to differentiate between colonization and active disease, and have described lower rates of CAPA amongst critically-ill patients (4.8% and 2%, respectively), but with a high colonization rate of 17.2% [14,15]. The high variability in the reported incidence of pulmonary aspergillosis in these patients [13-15] is mainly attributed to difficulties in defining the clinical relevance of *Aspergillus* in the respiratory tract and it's invasiveness [16] and to differences in corticosteroids use (dose and duration) during the course of the pandemic [17,18].

According to the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study

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group (EORTC/MSG) criteria, the diagnosis of invasive pulmonary aspergillosis (IPA), requires recovery of *Aspergillus* by culture from a sterile site, or a combination of host factors, including immunosuppression, typical pulmonary findings in imaging studies and a positive sputum culture or a biomarker such as galactomannan (GM) in serum or bronchoalveolar lavage (BAL) [19]. These criteria are difficult to apply in COVID-19 patients because classic host factors are not always present, typical radiological features are difficult to interpret, diagnostic bronchoscopies are not frequently performed and serum GM, which is relatively easy to measure, has decreased sensitivity for CAPA [8,9,16]. Therefore, new case definition criteria for CAPA were proposed by the European Confederation for Medical Mycology and the International Society for Human and Animal Mycology (ECMM/ISHAM) for "proven", "probable" or "possible" IPA in COVID-19 patients based on histological or microscopic evidence of *Aspergillus* or a positive GM test [17].

Evidence is also accumulating regarding invasive candidiasis, mainly candidemia, in COVID-19 patients, with a 2 to 10-fold increase in incidence compared to patients who do not have COVID-19 and an associated mortality as high as 72.7%–92.5% [20-22]. This is a higher rate compared to that commonly reported in intensive care unit (ICU) patients prior to the pandemic (51%–56.9%) [23,24].

This study aimed to assess the occurrence and outcomes of IFIs (both invasive *Aspergillus* infections and invasive candidiasis) in a database of critically ill COVID-19 patients admitted to the intensive care units at a large tertiary center and to define risk factors associated with IFI in these patients. The study was approved by the institutional research board (IRB) (approval number 0460–12-HMO).

2. Methods

This study was performed in three ICUs at the Hadassah-Hebrew University Medical Center in Jerusalem, Ein-Kerem Campus, a 900-bed inpatient tertiary hospital, serving a population of over one million people. Data were collected from patients' medical records during the second and third outbreaks of the COVID-19 epidemic in Israel (from 1 September to 30 November 2020 and 1 December to 31 March 2021, respectively).

2.1. Patients

Patients included were critically-ill adults with PCR-confirmed COVID-19 infection who during their course in the ICU had either:

1) documented invasive candidiasis 2) worsening respiratory function or infection that according to the clinical judgment of the treating physicians and infectious diseases team could represent pulmonary fungal infection and required evaluation of respiratory samples for *Aspergillus* growth or GM detection in respiratory samples and/or blood. Respiratory samples were aspirated through deep tracheal suction via either endotracheal tube or tracheostomy following blind instillation of 10–20 mL normal saline (non-bronchoscopic lavage, NBL), or via bronchoalveolar lavage (BAL), directed bronchsocopically.

In addition, for comparison purposes, we included consecutive COVID-19 critically-ill ICU patients who were admitted to the COVID-19 ICUs during the study period, had available data charts and who fulfilled only criteria 2 above.

2.2. Laboratory workup

Candida species were identified by the matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS, bioMerieux, Marcy, l'Etoile, France). *Aspergillus* spp. from respiratory samples that grew on routine media, were inoculated on Sabouraud dextrose agar (Novamed, Jerusalem, Israel) and following growth were identified morphologically by light microscopy or using the MALDI-TOF MS.

GM testing was performed using the Platelia™ *Aspergillus* seroassay in accordance with the manufacturer's instructions (Bio-Rad, Marnes-la-Coquette, France) and was considered positive if a single serum or respiratory sample OD cutoff was ≥1 [26], therefore, patients who had GM values between 0.5 and 1 were not included as "probable" CAPA, even though the new ECMM/ISHAM case-definition criteria allows serum GM cutoffs of >0.5 in probable cases [17].

2.3. Data

Demographic, clinical, and laboratory data of COVID-19 patients admitted to ICU were collected from patients' medical files (see Table 1). We used the highest Sequential Organ Failure Assessment (SOFA) score in the first 24 h of admission to ICU for analysis. Parameters were compared between patients with IFI and those without. Classification of CAPA was reviewed independently by the investigators of this study.

Table 1
Comparative data on the clinical characteristics and outcomes of COVID-19 critically-ill patients diagnosed with and without invasive fungal infection.

Variables	IFI	No IFI	*P* value
	N = 19	*N* = 55	
Clinical characteristics			
Female	4 (21%)	17 (31%)	0.61
Age above 75	11 (58%)	16 (29%)	0.05
Comorbidities			
CCI >3	16 (84%)	29 (53%)	0.02
Cardiovascular	15 (79%)	19 (35%)	0.002
Chronic lung disease	2 (11%)	5 (9%)	0.1
Neurological pathology	3 (16%)	4 (7%)	0.36
Chronic renal failure	7 (37%)	9 (16%)	0.1
Solid malignancy	0	3 (5%)	0.56
Hematological malignancy	3 (16%)	5 (9%)	0.415
Solid organ transplant	3 (16%)	2 (4%)	0.1
Other immunosuppression	3 (16%)	6 (11%)	0.68
ICU admission			
Septic shock[a]	15 (79%)	36 (65%)	0.42
Pneumonia	13 (68%)	48 (87%)	0.14
ARDS	18 (95%)	53 (96%)	1
Bacteremia	8 (42%)	25 (45%)	0.7
Abdominal infection	2 (11%)	2 (4%)	0.27
CPE/VRE carriage	6 (32%)	26 (47%)	0.35
Oxygen support	19 (100%)	54 (98%)	1
Mechanical ventilation	18 (94%)	54 (98%)	0.45
Invasive ventilation	18 (95%)	47 (85%)	0.54
Nitric oxide	7 (37%)	15 (27%)	0.61
ECMO	1 (5%)	5 (9%)	1
Inotropic support	17 (89%)	44 (80%)	0.58
Acute kidney injury	15 (79%)	32 (58%)	0.17
Acute liver failure	8 (42%)	8 (15%)	0.03
Blood transfusions >4	9 (47%)	8 (15%)	0.01
SOFA ≥11	6 (31%)	19 (35%)	1
Antimicrobial treatment			
Antifungals	12 (63%)	9 (16%)	<0.001
Carbapenem	14 (74%)	17 (31%)	0.002
Outcomes			
In hospital mortality	17 (89%)	33 (60%)	0.03
ICU LOS[b] (D) mean ± SD	30.7 ± 26.7	22.2 ± 14	0.2
COVID-19 associated ICU LOS[b] (D) mean ± SD	20.8 ± 13.5	15 ± 8.8	0.09
Ventilation days	29.8 ± 28.1	19.7 ± 14.8	0.15
Hospital LOS	47.5 ± 47.8	30.2 ± 16.1	0.14

IFI; invasive fungal infection, CCI; charlson comorbidity index, ICU; intensive care unit, ARDS; acute respiratory distress syndrome, CPE; carbapenemase-producing enterobacterales, VRE; vancomycin resistant enterococci, ECMO; extracorporeal membrane oxygenation, SOFA; sequential organ failure assessment, LOS; length of stay, D; days.

[a] Septic shock was defined as infection-related organ dysfunction who despite adequate fluid resuscitation, require vasopressors to maintain a mean arterial pressure ≥65 mmHg and have a lactate >2 mmol/L.

[b] Following recovery from COVID-19, 27/74 (25.6%) of the patients were transferred from COVID-19 ICU to medical or general ICU. "ICU LOS" refers to the total duration of stay in all ICUs.

2.4. Definitions

- Invasive candidiasis: Sterile body fluid/tissue positive for *Candida* species in culture or PCR test [19].
- Proven CAPA**:** At least one of the following: histopathological or direct microscopic detection of fungal hyphae in tissue, showing invasive growth with associated tissue damage; or *Aspergillus* recovered by culture, microscopy or histology obtained by a sterile aspiration or biopsy from a pulmonary site showing an infectious disease process [17].
- Probable CAPA: Tracheobronchial ulceration, nodule, pseudomembrane, plaque, or eschar seen on bronchoscopic analysis, or pulmonary infiltrate or cavitation preferably by chest computed tomography (CT), with one of the following: microscopic detection of true hyphae in BAL; positive BAL culture; serum or BAL GM ≥1 [17].
- Possible CAPA: Pulmonary infiltrate or cavitation preferably by chest CT, with at least one of the following obtained from NBL (blind application of 10–20 mL saline recovered by aspiration via the closed suction system in an intubated patient): microscopic detection of true hyphae; positive culture; single galactomannan >4·5; galactomannan >1·2 at least twice [17].
- *Aspergillus* respiratory colonization: All cases not fulfilling the criteria above.

2.5. Statistics

Categorical variables are presented with numbers and percentages and compared using Chri-square. Continuous variables are presented as means and standard deviations and compared using the Student *t*-test. We alsoexamined which characteristics were significantlyassociated with IFI using a logistic regression model including age, sex and ethnicity and additional variables found to be associated with IFI on univariate analysis. We considered *p*-values below 0.05 as statistically significant. Statistical analysis was done using SPSS software (IBM SPSS, Chicago, Illinois, version 24).

3. Results

During the study period, 3168 patients with a diagnosis of COVID-19 were admitted to our hospital. Of those, 311 were admitted to the ICUs (9.8%) and 19 were diagnosed with IFI (6.1%).

Eleven of the 311 patients admitted to ICUs (3.5%) had CAPA (5 possible and 6 probable) and 11 (3.5%) had candidemia: two with possible and one with probable CAPA (Supplementary Table S1). CAPA prevalence was 0.3% amongst all COVID-19 hospitalized patients during the study period.

Characteristics of 19 ICU-patients with COVID-19-associated IFI, compared to 55 COVID-19 ICU patients without IFI, are detailed in Table 1. In brief, patients with IFI were older (median age and IQR: 75 years and 66–80, compared with 67 years and 57–77, respectively), had more cardiovascular co-morbidity and a higher Charlson Comorbidity Index. Forty-seven percent of patients in both groups were immunocompromised due to malignancy, organ transplantation or immunosuppressive medications. Patients with IFI more frequently developed liver failure and received more blood transfusions. No difference in SOFA severity score was noted. Antifungals and carbapenem antibiotics were prescribed more frequently in IFI patients.

In-hospital mortality of patients with IFI was 89.4% (17/19) as compared to 60% (33/55) in patients without IFI ($p = 0.03$). Only one CAPA patient (probable CAPA) survived the hospitalization, but died 45 days post discharge. The in-hospital mortality of patients with candidemia was 90.9% (10/11). Six patients with IFI (6/19, 31.5%) did not receive antifungals (3 possible CAPA, 1 probable CAPA, 2 candidemia).

Multivariate analysis demonstrated that the most significant predictors of IFI were the existence of cardiovascular co-morbidity (OR 7.4 95% CI 1.5 to 36; $p = 0.01$) and the use of carbapenems (OR 13.7 95% CI 2.9 to 64; $p < 0.001$).

4. Discussion

The incidence of CAPA in this report was 3.5%, similar to later reports from different countries during the course of the epidemic [15]. Although we acknowledge that figures vary depending on geographic region, we think this rate reflects our and others' attempts to avoid over-diagnosis and misidentification of colonization as invasive infection, by searching for fungal invasive disease only in cases who were judged to have secondary infections, using respiratory cultures and GM. The classification of aspergillosis in COVID-19 patients is challenging, and it is increasingly recognized that criteria should not be limited to a single mycological evidence of IA (e.g positive respiratory culture) [16]. The recent CAPA diagnostic criteria endorsed by medical mycology societies [17] have tried to overcome this challenge, although arguments have been raised regarding the reliability of these criteria and differentiating between colonization and invasive disease [14]. Although the recent CAPA criteria consider a serum GM cutoff above 0.5 as positive for defining probable CAPA cases [17], we used a higher cutoff of ≥1, similar to that determined by the EORTC/MSG for probable IPA [19], to further avoid inclusion of false-positive cases. The link between other viruses such as influenza and invasive aspergillosis has been well established during the last decade [27,28]. The incidence of Influenza-associated pulmonary aspergillosis (IAPA) varies considerably in different countries and in different seasons (0–23%) [29]. Factors that contribute to regional differences in both IAPA and CAPA are underlying chronic medical conditions, exposure to corticosteroids, relying solely on the use of non-culture based methods such as GM for diagnosis, the use of different cut-offs, and environmental factors [30]. Of note, there were no cases of other mold infections amongst these patients in spite of increasing reports of rhino-orbital mucormycosis in COVID-19 patients globally [31,32].

In contrast to pulmonary aspergillosis, which was mainly associated with influenza pneumonia in ICUs before 2019, candidemia is considered one of the most common bloodstream infections in ICUs [33]. In our institution, the incidence of candidemia (per 1000 admissions per year) in non-COVID-19 ICU patients is 1.7% [34], lower than the 3.5% found in COVID-19 ICU patients. Other studies have also reported an increase in candidemia in patients with COVID-19 compared to non-COVID-19 patients [21,22,35]. This increase is not surprising result due to the increased exposure of COVID-19 patients to risk factors associated with candidemia, such as the need for corticosteroids use, the multisystem involvement of the disease resulting in a complicated and prolonged clinical courses, as well as the increased use of broad-spectrum antibiotics [21,22,35].

The high mortality rate associated with candidemia in this study (90.9%), is higher than that reported in previous COVID-19 studies [21,22,35], although a recent study that included only ICU patients also found a very high rate (92.5%) [20]. This high mortality rate may be associated with the complicated medical background and clinical course of COVID-19 patients in ICUs. In comparison, other reported rates of non-COVID-19 candidemia-associated mortality from ICUs worldwide is lower and ranges between 51% and 56.9% [23,24]. Nevertheless, most of the patients in our cohort (97%), were ventilated mechanically, therefore, the high mortality rate associated with candidemia, may be attributed to the higher mortality reported in COVID-19 patients that require mechanical ventilation, as compared with other ICU patients (50–97% vs 35–46%, respectively) [2,36,37]. Of note, the in-hospital mortality associated generally with IFI (both candidemia and CAPA) was markedly increased as compared to those without IFI (89% vs 60%, $p < 0.03$) though most of the patients in both groups were mechanically ventilated (94% vs 98%, $p < 0.45$). This finding exemplifies the high mortality associated with CAPA, also previously reported in other studies [38]. All the patients in this study received

high dose corticosteroids, that are known to cause cellular immunodeficiency and predispose patients to both invasive candidemia and IA [39]. In contrast to other studies [20], we did not find the use of corticosteroids to be independently associated with IFI although we did not examine the duration of corticosteroid treatment.

Understanding the risk factors for development of IFI is important, to be able to identify and treat high-risk patients early. We found older age (>75 y) and co-morbidities (reflected by a high Charlson Comorbidity Index score), as well as a clinical course including liver failure, increased use of blood transfusions, carbapenems and antifungals, to be associated with an increased incidence of IFI. Older age and co-morbidities were also found to be risk factors for IFI in other studies [40]. We think these variables primarily reflect patients with more severe COVID-19 with prolonged ICU stay, that predispose them to secondary infections. In multivariate analysis, only cardiovascular co-morbidity and carbapenem use were found to be independent risk factors for IFI. As the first may reflect a complicated ICU course, the latter is associated with suppression of the normal microbiota with consequent colonization and translocation of *Candida* into the bloodstream [41]. This association was also reported in other studies showing an increased risk for IAPA [42]. These findings underscore the necessity for antibiotic stewardship in COVID-19 critically ill patients.

Some of the patients with IFI did not receive antifungal treatment because they died before the diagnosis was made. Kayaaslan et al. [20] have pointed to the relatively early appearance of candidemia in critically-ill COVID-19 patients that may be related to the early use of corticosteroids, and suggested that candidemia doesn't readily come to mind as a diagnosis in the early period of infection. A timely diagnosis and treatment is known to be related to improved survival [43].

The limitations of this study are that it was a retrospective study based on data from a single center and the evidence of CAPA is not tissue-proven, though the latter is a general limitation of pulmonary aspergillosis diagnosis. In addition, NBLwas commonly used in the study patients to obtain respiratory samples, instead of bronchoscopic BAL which is the preferred method to reduce airway contamination and obtain deep alveolar samples. Nevertheless, former studies demonstrated a strong correlation between the isolation rates of pathogens using both methods [44]. The relatively small sample size and control group limits exact risk estimation of IFI amongst COVID-19 patients.

In conclusion, we found a low incidence of CAPA in COVID-19 critically ill patients, in line with recently reported studies, which emphasizes the need to differentiate between true infection and colonization in high-risk patients. The increase in candidemia cases observed was expected due to increased exposure of COVID-19 patients to risk factors traditionally associated with candidemia. The use of broad-spectrum antibiotics in these patients should be monitored and strictly limited, as carbapenems were found to be an independent risk factor for IFIs. Awareness and timely diagnosis of IFIs in COVID-19 critically ill patients are imperative, considering the high mortality associated with this condition.

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CrediT authorship contribution statement

Oshrat Ayalon: Data curation, Investigation, Methodology, Investigation, Data curation, Writing – original draft. **Matan J. Cohen:** Data analysis, Software, Validation, Formal analysis. **Efrat Orenbuch-Harroch:** Validation, Investigation. **Sigal Sviri:** Methodology, Resources, Writing – review & editing. **Peter Vernon van Heerden:** Methodology, Resources, Writing – review & editing. **Maya Korem:** Conceptualization, Methodology, Validation, Resources, Writing – review & editing, Supervision.

Declaration of Competing Interest

The authors declare none.

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