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Risk factors and outcomes of fungal superinfections in patients with severe COVID-19: an observational study from Pisa academic hospital

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SUMMARY

Background: Superinfections acquired during the hospital course represent common complications in COVID-19 patients. Several studies reported an increasing incidence of COVID-19 associated pulmonary aspergillosis (CAPA) and candidaemia. The aim of this study is to describe fungal superinfections in a large cohort of hospitalized patients with COVID-19 and identify factors independently associated with the risk of fungal superinfections.
Methods: Observational study including patients with COVID-19 admitted to the tertiary-care, University Hospital of Pisa, Italy from April 2020 to May 2021. Patients with pneumonia and laboratory confirmed SARS-CoV-2 infection with a RT-PCR test on a nasopharyngeal swab, were eligible for the study. Patients who died within 24 hours from admission and those with missing data were excluded. Data about fungal superinfections were collected. To identify factors independently associated with the development of fungal superinfections, a multivariate regression analysis was performed.
Results: Among 983 patients with COVID-19, 52 (5.3%) fungal superinfections were detected. Fungal superinfections included: 24/52 (46%) CAPA, 27/52 (51.9%) episodes of candidaemia and 1 case of pulmonary pneumocystosis in a haematological patient. All patients with CAPA were cared for in intensive care unit (ICU). The majority of patients received liposomal amphotericin B as antifungal treatment (83.3%). In-hospital mortality was 41.7%. Among 27 episodes of candidaemia, 16 (59.3%) occurred in ICU while 11 (40.7%) in medical wards. In-hospital mortality was 14.8%. Overall, patients with fungal superinfections had a median age of 73 (IQRs 59-77) years and a median length of ICU stay of 40 (17-50) days. In-hospital mortality among all patients with superinfections was 28.8%. On multivariable analysis, ICU stay (OR 17.63, 95% CI 8.3-37.41, p<0.001), high-dose steroids (OR 13.48, 95% CI 6.68-27.26, p<0.001), and diabetes mellitus (OR 2.14, 95% CI 1.09-4.17, p=0.026) were factors independently associated with the risk of developing a fungal superinfection.
Conclusions: Fungal superinfections may complicate the hospital course of COVID-19 patients, especially of those admitted to ICU. Surveillance with detection of galactomannan on bronchoalveolar lavage in patients with clinical deterioration should be performed. A rational use of steroids is essential to avoid the risk of developing a fungal superinfection.

Keywords: Fungal infections, pulmonary aspergillosis, candidemia, COVID-19, SARS-CoV-2.

INTRODUCTION

The COVID-19 pandemic has overwhelmed healthcare facilities and raised new concern about the management of hospitalized patients. Superinfections acquired during the hospital

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course represent common complications in COVID-19 patients and are prevalent, but not limited to, intensive care settings [1-4]. It has been demonstrated that bacterial superinfections lead to prolonged length of hospital stay as well as concern about nosocomial transmission of resistant organisms [1]. However, there is raising concern about an increase in fungal infections among COVID-19 patients.
Since the start of the pandemic, coronavirus associated pulmonary aspergillosis (CAPA) has been reported as a severe complication of patients undergoing invasive mechanical ventilation [5]. Several studies reported heterogeneous data about CAPA with a prevalence ranging from less that 5% up to 30% according to disease severity, setting of care, use of surveillance programs and different diagnostic criteria [6, 7].
Not only CAPA but also other fungal infections may complicate the course of COVID-19. Several recent studies reported an increasing incidence of candidaemia among COVID-19 patients [8-12]. Finally, other less common fungal infections, including pneumocystosis and mucormycosis, have been described in patients with severe COVID-19 [13-15].
The aim of this study was to describe clinical characteristics and outcome of hospitalized patients with COVID-19 who developed fungal superinfections.

PATIENTS AND METHODS

Ethics
The research was conducted in accordance the Declaration of Helsinki and national and institutional standards. The Internal Review Board (IRB) of the Comitato Etico Area Nord-Ovest (CEAVNO) approved the study (approval number 17681) and a written informed consent was obtained from study participants.

Study design and definitions
This is a single-centre observational study including patients with COVID-19 admitted to the tertiary-care, University Hospital of Pisa, Italy from April 2020 to May 2021. Patients with pneumonia and laboratory confirmed SARS-CoV-2 infection with a RT-PCR test on a nasopharyngeal swab, were eligible for the study. Only patients with available data about study variables were included in the final analysis. We excluded patients who died within 24 hours from hospital admission and those who did not provide informed consent.
Since during the study period there was limited evidence for any anti-COVID-19 treatment, the patients were treated according to an internal guide for the management of COVID-19 patients elaborated by a panel of experts (infectious diseases physicians, pneumologists, microbiologists, emergency medicine experts, intensivists). Treatment strategies have been previously detailed [16]. Immunomodulant agents used for patients with severe COVID-19 were tocilizumab and baricitinib. The decision to prescribe one of the 2 immunosuppressants was made by the attending physician. Tocilizumab was used at the dosage of 400 mg ev, followed by a second administration of 400 mg ev after 24 hours. Baricitinib was administered at a dose of 4 mg/day for 14 days [17]. The use of steroids was classified in low and high dose based on the cut-off of 1 mg/kg/day of methylprednisolone or equivalents [18].
All patients were prospectively followed-up: a dedicated staff of research fellows identified patients with SARS-CoV-2 pneumonia as soon as they arrived at the Emergency Department, followed the patients during the hospital stay and collected all data prospectively without interfering with the therapeutic decisions. Epidemiological and demographic information, medical history, co-morbidities, information on clinical symptoms at admission, treatments received during the hospital course were collected.
All fungal superinfections were described. Superinfections were defined as infections occurred 48 hours after admission for COVID-19 [1]. CAPA was diagnosed according to proposed criteria [19,20]. A diagnostic workup was adopted in clinically deteriorating patients with no other explanation or with cavitary and/or nodular lesions on CT scan. In these cases, bronchoscopy with bronchoalveolar lavage was performed according to judgment of infectious disease consultant. Microbiological investigations including culture, GM and Aspergillus PCR were performed on BAL samples. CAPA was defined according to the recently proposed CAPA definition consisting in COVID-19 positive patients with pulmonary infiltrates (entry criterion) who had positive GM index (serum GM index >0.5 or BAL GM index >1.0) [20]. The galactomannan antigen index was mea-

sured with a sandwich enzyme-linked immunosorbent assay (ELISA) in BALs and serum specimens. Candidaemia was defined by at least 1 positive blood culture yielding *Candida* spp. in a patient with fever and/or other clinical signs of infection [21, 22].
Fungal identification on positive blood cultures was performed by microscopic examination of lactophenol cotton-blue stained slides and by MALDI-TOF Mass Spectrometry Instrument (Bruker, Italy), following manufacturer's instructions.

Study outcome
The primary objective was to describe clinical characteristics of fungal superinfections in hospitalized patients with COVID-19.
The secondary objective was to identify factors independently associated with the development of fungal superinfections.

Statistical analysis
Continuous and categorical variables were presented as median (IQR) and absolute number (percentage), respectively. The Mann-Whitney U-test, χ^2 test and Fisher's exact test were used to compare differences between groups.
According to the study outcome, we performed a comparison between patients who developed fungal superinfections during the hospital stay and those who did not. To identify factors independently associated with the development of fungal superinfections, a multivariable regression analysis was performed. The multivariable analysis using logistic regression prediction models was constructed using a forward stepwise procedure, entering all variables with univariate $p<0.05$. Collinearity among the variables was calculated on the basis of the variance inflation factor (VIF). Variables with collinearity and those clinically correlated each other were not entered. The final multivariate model was chosen according to the Akaike information criterion and to parsimony and clinical interpretability of data. Statistical significance was established at $p<0.05$. All reported p values are two tailed. The results obtained were analyzed using a commercially available statistical software package (SPSS 27.0; IBM, Armonk, NY, USA).

RESULTS

Among 983 patients with COVID-19, 52 (5.3%) fungal superinfections were detected. Fungal superinfections included: 24/52 (46%) CAPA, 27/52 (51.9%) episodes of candidaemia and 1 case of pulmonary pneumocystosis in a haematological patient. Among patients hospitalized in ICU (n=253), CAPA occurred in 9.5% (24/253) and candidaemia in 6.3% (16/253) of patients (Figure 1). Among intubated patients (n=122), CAPA occurred in 13.9% (17/122) and candidaemia in 12.3% (15/122) of patients.
Characteristics of the 24 patients with CAPA and COVID-19 associated candidaemia are reported in Table 1. All patients were cared for in ICU. Five (20.8%) patients underwent extracorporeal membrane oxygenation support (ECMO). The majority

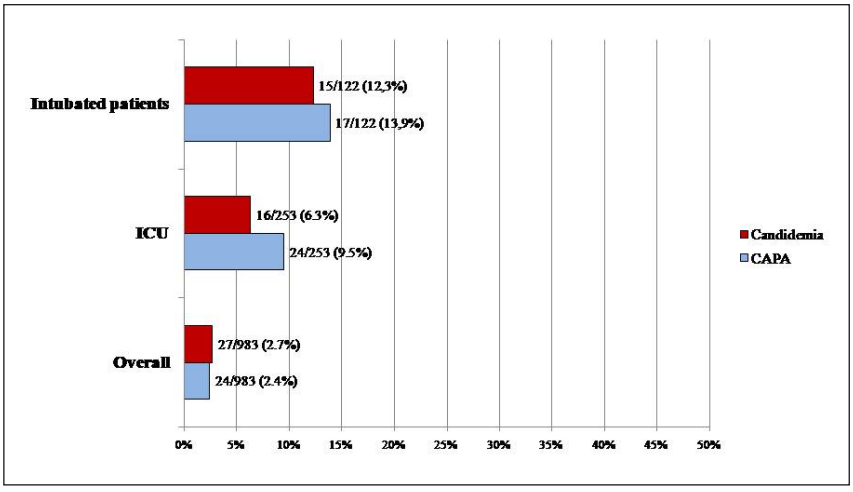

Figure 1 - Distribution of fungal superinfections in COVID-19 patients hospitalized in all type of wards and in ICU.

Table 1 - Clinical characteristics and outcomes of patients with CAPA and candidaemia.

Characteristics	*CAPA N=24*	*Covid-19 associated candidemia N=27*
Demographics		
Age, median (IQRs)	59.5 (55-75.5)	76 (68-79)
Male sex	20 (83.3%)	19 (70.4%)
Underlying diseases		
Hypertension	2 (8.3%)	15 (55.6%)
Diabetes mellitus	18 (75%)	5 (18.5%)
Cardiovascular disease	8 (33.3%)	12 (44.4%)
COPD	6 (25%)	6 (22.2%)
CKD	4 (16.7%)	3 (11.1%)
Solid cancer	0	3 (11.1%)
ICU stay	24 (100%)	16 (59.3%)
Non-invasive mechanical ventilation	5 (20.8%)	4 (14.8%)
Invasive mechanical ventilation	17 (70.8%)	15 (55.6%)
Covid-19 treatment		
Steroids	24 (100%)	18 (66.7%)
High dose steroids	18 (75%)	11 (40.7%)
IL-6 or JAK inhibitors	20 (83.3%)	7 (25.9%)
ECMO	5 (20.8%)	0
Length of hospital stay	49 (25-57.5)	25 (17-31)
Length of ICU stay after CAPA diagnosis	45 (45 (28-49)	19 (17-25)
In-hospital mortality	10 (41.7%)	4 (14.8%)
CAPA Treatment		
Azoles*	4 (16.7%)	7 (25.9%)
Liposomal amphotericin B	20 (83.3%)	6 (22.2%)
Echinocandins		14 (51.8%)

* Patients with CAPA were treated with isavuconazole.
CAPA: COVID-19 associated pulmonary aspergillosis; COPD: chronic obstructive pulmonary disease; CKD: chronic kidney disease; ECMO extracorporeal membrane oxygenation support; ICU: intensive care unit.

of patients received liposomal amphotericin B as antifungal treatment (83.3%). In-hospital mortality was 41.7%.

Among 27 episodes of candidaemia, 16 (59.3%) occurred in ICU while 11 (40.7%) in medical wards. The most common *Candida* species was *Candida albicans* (13/27, 48.1%), followed by *Candida parapsilosis* (12/27, 44.4%), *Candida glabrata* (1/27, 3.7%) and *Candida tropicalis* (1/27, 3.7%). Overall, 15 (55.6%) episodes were CVC-related candidaemia, while in the remaining 12 (44.4%) source of candidaemia remained unknown. The majority of patients were intubated (55.6%). In-hospital mortality was 14.8%.

Among all patients with fungal superinfection, median age was 73 (IQRs 59-77) years and the majority of patients were males (76.9%). Median length of ICU stay was 40 (17-50) days. In-hospital mortality among patients with superinfections was 28.8% (15/52 patients).

Comparison of patients with fungal superinfections and those without is reported in Table 2. Patients who developed fungal superinfections were more frequently cared for in ICU and underwent more commonly invasive mechanical ventilation. Immunomodulant agents, including IL-6 and JAK inhibitors, were more common in patients who developed fungal infections. Length of ICU stay was longer in patients with fungal superinfections than in controls.

On multivariate analysis, ICU stay (OR 17.63, 95% CI 8.3-37.41, p<0.001), high-dose steroids (OR 13.48, 95% CI 6.68-27.26, p<0.001), and diabetes mellitus (OR 2.14, 95% CI 1.09-4.17, p=0.026) were factors independently associated with the risk of developing a fungal superinfection (Table 3).

Table 2 - Comparison of COVID-19 patients who developed fungal superinfections and those who did not.

Characteristics	*Controls N=931*	*Fungal superinfections N=52*	*p*
Demographics			
Age, median (IQRs)	68 (57-79)	73 (59-77)	0.637
Male sex	40 (76.9%)	599 (64.3%)	0.064
Underlying diseases			
Hypertension	430 (46.2%)	17 (32.7%)	0.057
Diabetes mellitus	214 (23%)	23 (44.2%)	<0.001
Cardiovascular disease	287 (30.8%)	20 (38.5%)	0.248
COPD	100 (10.8%)	12 (23.1%)	0.007
CKD	67 (7.2%)	7 (13.5%)	0.096
Solid cancer	100 (10.8%)	3 (5.8%)	0.254
ICU stay	213 (22.9%)	40 (76.9%)	<0.001
High flow nasal cannula			
Non-invasive mechanical ventilation	222 (23.8%)	9 (17.3%)	0.279
Invasive mechanical ventilation	90 (9.7%)	32 (61.5%)	<0.001
Covid-19 treatment			
Steroids	673 (72.3%)	43 (82.7%)	0.101
High dose steroids	129 (13.9%)	29 (55.8%)	<0.001
IL-6 or JAK inhibitors	153 (16.4%)	27 (51.9%)	<0.001
ECMO	25 (2.7%)	5 (9.6%)	0.005
Length of hospitalization	14 (9-22)	45 (27.5-49)	<0.001
Length of ICU stay	0 (0-5)	40 (17-50)	<0.001
In-hospital mortality	89 (9.6%)	15 (28.8%)	<0.001

COPD: chronic obstructive pulmonary disease; CKD: chronic kidney disease; ECMO extracorporeal membrane oxygenation support, ICU: intensive care unit.

Table 3 - Multivariable analysis of factors independently associated with fungal superinfections.

	OR (95% CI)	*p value*
ICU stay	17.63 (8.3-37.41)	<0.001
High-dose steroids	13.48 (6.68-27.26)	<0.001
Diabetes mellitus	2.14 (1.09-4.17)	0.026

DISCUSSION

In this observational study, we described clinical characteristics and outcomes of COVID-19 patients who developed fungal superinfections during their hospital stay. Of importance, we found that the majority of fungal superinfections occurred in ICU and length of stay may be prolonged in patients with fungal infections. Co-morbidities, including diabetes mellitus, and the use of high-dose steroids are factors increasing the risk of fungal superinfections. Since the start of the pandemic, there was concern about the development of CAPA among patients with severe COVID-19 [7]. Although invasive aspergillosis has been traditionally considered an infection occurring in patients with well established risk factors, such as neutropenia, hematologic malignancies, organ transplantation, or HIV, some cases have been reported in special patients' populations [23]. Pulmonary aspergillosis has been described as a potential complication of influenza [24]. In fact, it is known that viruses, like influenza, may induce alveolar epithelial and endothelial damage, impaired muco-ciliary function and immune cell dysregulation favoring the development of fungal superinfections [25]. In presence of a systematic surveillance program, CAPA was diagnosed in 27.7% of patients with COVID-19 [7]. However, there is a great heterogeneity in the prevalence of this clinical entity. This heterogeneity is also due to several reasons. First, disease severity affects the risk of CAPA. A recent review highlighted that pulmonary aspergillosis may complicate COVID-19 in 8.9% of patients admitted to the ICU and in 20.1% of those requiring invasive ventilation [5]. Second, the prevalence rates varied widely due to the fact that CAPA was, and still remains, challenging to diagnose in patients with COVID-19. There was reluctance to perform bronchoscopies and some studies relied on unspecific myco-

logical evidence, such as culture growth or non-validated GM detection in tracheal aspirate. These circumstances, combined with the unspecific clinical and radiological presentation of CAPA in patients with COVID-19, contributed to the high variability observed across studies. Third, absence of uniform consensus criteria in the early phases of the pandemic impacted on the reported prevalence data. More recent diagnostic criteria underline the role of validated GM on BAL to discriminate between airway colonization and pulmonary aspergillosis. Thus, a better diagnostic approach is essential in guiding the clinician to an evidence-based decision between early treatment or a "wait and see" strategy [5]. Clinical suspicion based on risk factors together with GM detection on BAL should guide the therapeutic strategy in patients with COVID-19. In our study, we found that 9.5% of patients hospitalized in ICU and 13.9% of intubated patients developed CAPA based on current diagnostic criteria. This may be due to the lack of systematic surveillance on BAL, but our data reflect the real-world practice in which patients with clinical suspicion of CAPA and deterioration of respiratory function undergo GM detection on BAL. We observed a high in-hospital mortality rates in patients with CAPA, but it should be considered that patients with CAPA had a high disease severity.

Candidaemia episodes have been increasingly reported in COVID-19 patients. In a recent observational study including 275 hospitalized patients with COVID-19, 101 *Candida* isolates identified in the 91 case patients with candidaemia were reported [8]. Of importance, in-hospital mortality was significantly higher in patients who developed candidaemia than in those who did not [8]. This led some authors to develop a score specifically derivated in patients with COVID-19 (CAC-Score) to help clinicians in the early identification of patients with candidaemia [9]. In our cohort of patients, there was a consistent prevalence of *C. parapsilosis* isolates. A recent study conducted in Spain showed that the incidence of candidaemia caused by fluconazole-resistant *C. parapsilosis* increased significantly in the pandemic period [12]. Although this increasing prevalence may reflect the local epidemiology, it should be acknowledged that *C. parapsilosis* are associated with indwelling catheters due to their ability to form biofilm on the surfaces of intravascular devices and on the hands of healthcare workers [26]. These findings highlight the need of implementation of infection control procedures in COVID-19 wards.

Of importance, the use of high dose of steroids increase the risk of fungal superinfections. There is controversy about the use of high-dose of steroids. Dexamethasone 20 mg/day from day 1 to 5 and 10 mg/day from day 6 to 10 in severe COVID-19 showed no clinical benefit [27]. Thus, high dose of steroids should be avoided in patients with severe COVID-19 and attention should be paid to patients who received both steroids and immunomodulant agents.

This study has some limitations. First, the decision to perform or not BAL was based on clinical judgment by attending physician together with the suggestion of the infectious diseases' consultant. This may have led to an underestimation of CAPA, but our diagnostic workup represents a real-world approach that combined clinical suspicion and GM detection on BAL in selected cases. The role of infectious diseases' consultant may have a pivotal role in selecting patients who need BAL to exclude CAPA. Second, our experience may depend on local epidemiology and might not be generalizable to all ICU settings in other countries. Finally, our study has been conducted before the spread of new variants of concern and include also patients before the vaccination campaign. The prevalence and the outcomes of fungal superinfections in patients affected by the new variants may vary from those reported.

In conclusion, we reported that about 5.3% of COVID-19 patients developed a fungal superinfection. This prevalence is higher if we consider only patients cared for in ICU. CAPA and COVID-19 associated candidaemia represent the most frequent fungal superinfections in COVID-19 patients. A rational use of steroids is essential to avoid the risk of developing a fungal superinfection.

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Declaration of interest statement

MF received speakers' honoraria from Angelini, MSD, Pfizer, and Nordic Pharma. FM has participated in advisory boards and/or received speaker honoraria from Angelini, Correvio, MSD, Pfizer, Astellas, Gilead, BMS, Jansenn, ViiV, bioMérieux,

Biotest, Becton-Dickinson, Nordic Pharma, Pfizer, Shionogi. All COI are outside the submitted study.

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