Fungal infections in mechanically ventilated patients with COVID-19 during the first wave: the French multicentre MYCOVID study

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Summary

Background Patients with severe COVID-19 have emerged as a population at high risk of invasive fungal infections (IFIs). However, to our knowledge, the prevalence of IFIs has not yet been assessed in large populations of mechanically ventilated patients. We aimed to identify the prevalence, risk factors, and mortality associated with IFIs in mechanically ventilated patients with COVID-19 under intensive care.

Methods We performed a national, multicentre, observational cohort study in 18 French intensive care units (ICUs). We retrospectively and prospectively enrolled adult patients (aged ≥18 years) with RT-PCR-confirmed SARS-CoV-2 infection and requiring mechanical ventilation for acute respiratory distress syndrome, with all demographic and clinical and biological follow-up data anonymised and collected from electronic case report forms. Patients were systematically screened for respiratory fungal microorganisms once or twice a week during the period of mechanical ventilation up to ICU discharge. The primary outcome was the prevalence of IFIs in all eligible participants with a minimum of three microbiological samples screened during ICU admission, with proven or probable (pr/pb) COVID-19-associated pulmonary aspergillosis (CAPA) classified according to the recent ECMM/ISHAM definitions. Secondary outcomes were risk factors of pr/pb CAPA, ICU mortality between the pr/pb CAPA and non-pr/pb CAPA groups, and associations of pr/pb CAPA and related variables with ICU mortality, identified by regression models. The MYCOVID study is registered with ClinicalTrials.gov, NCT04368221.

Findings Between Feb 29 and July 9, 2020, we enrolled 565 mechanically ventilated patients with COVID-19. 509 patients with at least three screening samples were analysed (mean age 59·4 years [SD 12·5], 400 [79%] men). 128 (25%) patients had 138 episodes of pr/pb or possible IFIs. 76 (15%) patients fulfilled the criteria for pr/pb CAPA. According to multivariate analysis, age older than 62 years (odds ratio [OR] 2·34 [95% CI 1·39–3·92], p=0·0013), treatment with dexamethasone and anti-IL-6 (OR 2·71 [1·12–6·56], p=0·027), and long duration of mechanical ventilation (>14 days; OR 2·16 [1·14–4·09], p=0·019) were independently associated with pr/pb CAPA. 38 (7%) patients had one or more other pr/pb IFIs: 32 (6%) had candidaemia, six (1%) had invasive mucormycosis, and one (<1%) had invasive fusariosis. Multivariate analysis of associations with death, adjusted for candidaemia, for the 509 patients identified three significant factors: age older than 62 years (hazard ratio [HR] 1·71 [95% CI 1·26–2·32], p=0·0005), solid organ transplantation (HR 2·46 [1·53–3·95], p=0·0002), and pr/pb CAPA (HR 1·45 [95% CI 1·03–2·03], p=0·033). At time of ICU discharge, survival curves showed that overall ICU mortality was significantly higher in patients with pr/pb CAPA than in those without, at 61·8% (95% CI 50·0–72·8) versus 32·1% (27·7–36·7; p<0·0001).

Interpretation This study shows the high prevalence of invasive pulmonary aspergillosis and candidaemia and high mortality associated with pr/pb CAPA in mechanically ventilated patients with COVID-19. These findings highlight the need for active surveillance of fungal pathogens in patients with severe COVID-19.

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Research in context

Evidence before this study

Patients with severe viral respiratory infection caused by influenza have been shown to be at high risk of acute respiratory distress syndrome (ARDS) and prone to develop invasive pulmonary aspergillosis (IPA). SARS-CoV-2 infection can also lead to severe ARDS, for which mechanical ventilation is required. Patients with COVID-19 might thus also be at risk of developing invasive fungal infections (IFIs), including invasive aspergillosis (ie, COVID-19-associated invasive aspergillosis; CAPA), for which consensus criteria for research and clinical guidance were published in *The Lancet Infectious Diseases* in 2020. We searched the PubMed database, using the terms "COVID-19" AND ("aspergillosis" OR "candidaemia" OR "fungal infections"), to find studies that investigated the prevalence and risk factors of fungal co-infections in patients with COVID-19 published between Nov 1, 2019, and Sept 30, 2020. Only small cohort studies and case-reports have been published and variable prevalence of IFI was reported. We identified no active surveillance studies that had evaluated the prevalence, risk factors, and outcomes of IFIs in a large, homogeneous, high-risk population of patients with COVID-19 and acute respiratory distress syndrome or requiring mechanical ventilation in the intensive care unit (ICU).

Added value of this study

To our knowledge, this study included the largest cohort of patients to be systematically screened for IFIs, enrolling 565 mechanically ventilated patients with COVID-19 in the ICU. First, we found a high number of cases of proven or probable (pr/pb) IFIs (114 [22%] of 509 patients analysed). Second, IPA and candidaemia were the most frequent IFIs. The overall prevalence of pr/pb CAPA, based on the recently published case definition, was 15%, and 6% for candidaemia. Third, this study found a high mortality among patients with pr/pb CAPA, of 61·8% (95% CI 50·0–72·8), versus 32·1% (27·7–36·7) for the non-pr/pb CAPA group, and patients with pr/pb CAPA had an independently higher risk of death (hazard ratio 1·45 [95% CI 1·03–2·03]) than those without. Of note, a high mortality of 45·8% (95% CI 25·6–67·2) was also observed in 24 (5%) patients with non-bronchoalveolar lavage or bronchial or tracheal aspiration positive for *Aspergillus* spp and a compatible clinical context of aspergillosis, compared with non-CAPA patients. Finally, we found that the combination of dexamethasone and anti-interleukin-6 for SARS-CoV-2 infection was significantly associated with pr/pb CAPA (odds ratio 2·71 [95% CI 1·12–6·56], which is a milestone with regard to the management of patients with COVID-19.

Implications of all the available evidence

The high prevalence and mortality associated with IFIs, particularly invasive aspergillosis and candidaemia, highlight the need for a high index of suspicion for patients with severe COVID-19 in the ICU, and an urgent necessity of implementing active surveillance. Further studies are required to establish whether early antifungal treatment or prophylaxis is needed in patients at high risk of IFIs.

Introduction

Fungal infections are known to be among the infectious complications related to the damage caused by viral pulmonary infections, particularly in patients admitted to intensive care units (ICUs) with severe acute respiratory distress syndrome (ARDS). Indeed, invasive pulmonary aspergillosis (IPA) is now a well known complication of the clinical course of critically ill patients with influenza.[1,2] Patients with severe COVID-19 have also emerged as a population with a high risk of fungal infections.[3,4] COVID-19 is associated with epithelial lung damage, lymphopenia, dysfunction of the cell immune response, and the use of broad spectrum antibiotics, dexamethasone, and immunosuppressive therapies.[5] Thus, adhesion of *Aspergillus* spp spores (conidia) might be promoted by previous damage of the lungs due to SARS-CoV-2 infection and multiple risk factors could lead to tissue invasion after conidia germination.[6,7]

During the COVID-19 pandemic, several case series have been published that suggest an increased risk of IPA in patients with severe COVID-19 (ie, COVID-19-associated pulmonary aspergillosis; CAPA), with an estimated prevalence of less than 5% to greater than 30% depending on several factors, whereas the prevalence of candidaemia and other fungal infections remains poorly understood.[5] However, the heterogeneity of monitoring protocols, diagnostic tools, and severity of COVID-19 cases in previous studies (all hospitalised patients, only patients in the ICU, or only patients in the ICU with ARDS) create difficulties in interpreting published data.

Only recently have specific criteria for the case definition and diagnosis of CAPA been published.[8] Consensus recommendations are essential because patients who have been infected during the pandemic do not meet the usual criteria of 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 Group for invasive aspergillosis, as no host-related risk factors or specific clinical features are evident in COVID-19 patients with IPA.[9] In addition, the more focused aspergillosis algorithm (AspICU) to diagnose IPA in critically ill patients does not include new diagnostic developments and appears to be ill-adapted to patients with COVID-19.[10] Furthermore, the typical radiological features of aspergillosis might be difficult to assess in ARDS-associated COVID-19,[11] highlighting the importance of a multidisciplinary approach for the diagnosis and management of IPA in patients with COVID-19.

The MYCOVID study sought to characterise the prevalence, risk factors, and outcome of invasive fungal infections (IFIs), including IPA and candidaemia, in

mechanically ventilated patients with COVID-19 in the ICU, with use of standardised procedures.

Methods

Study design and participants

We performed a national, multicentre, observational cohort study in 18 participating university hospital ICUs across France (appendix p 5). Adult patients (aged ≥18 years) were eligible for enrolment if they had a diagnosis of SARS-CoV-2 infection confirmed by quantitative RT-PCR, and required mechanical ventilation for ARDS. ARDS was defined in accordance with international guidelines proposed by the consensual ARDS Definition Task Force.[12] Patients were consecutively retrospectively and prospectively included. Retrospective data collection began on Feb 29, 2020. The patients' clinical and biological data were collected as part of their follow-up from admission to discharge from the ICU. Data were collected anonymously in the present study and managed with electronic case report forms (eCRFs).

The MYCOVID study was conducted in full concordance with the principles of the Declaration of Helsinki and the French laws and regulations of France. This study was approved by the French authorities (Comité Consultatif sur le Traitement de l'information en matière de Recherche dans le domaine de la Santé, and Commission Nationale de L'Informatique et des Libertés). According to French policy, a non-opposition statement was obtained from all included patients signifying that all received written detailed information about the objectives of the study and were free to request withdrawal of their data at any time. The study protocol was reviewed and approved by the ethics committee of Rennes University Hospital, Rennes, France (approval number 20.56). The study is registered with ClinicalTrials.gov, NCT04368221.

Procedures

In each participating ICU, patients were systematically screened for respiratory fungal microorganisms once or twice a week during the period of mechanical ventilation up to ICU discharge, resulting in a minimum of three samples if discharge occurred after 15 days (appendix p 8). Respiratory samples included any combination of bronchoalveolar lavage, non-bronchoscopic lavage, tracheal aspiration, and bronchial aspiration. The local microbiological laboratory in each participating centre processed fungal cultures of the samples. Real-time quantitative PCR (qPCR) for *Aspergillus* spp, *Pneumocystis jirovecii*, and Mucorales was also performed on the same samples, either locally or following referral to a specialised laboratory. Other microbiology sampling and tests were performed according to the local ICU hospital standard of care. Specific blood biomarkers (qPCR for either *Aspergillus* spp or Mucorales, galactomannan, and 1, 3-β-D-glucan antigenemia) were sought if respiratory samples were positive either for filamentous fungi or *P jirovecii*. Demographic and clinical data, including underlying diseases, clinical severity scores (Simplified Acute Physiology Score [SAPS] II and Sequential Organ Failure Assessment [SOFA]), anti-COVID-19 treatments, laboratory data (lymphopenia, viral detection of herpes simplex virus type 1 [HSV-1] and cytomegalovirus [CMV], bacterial and fungal ventilator-associated pneumonia [VAP], and candidaemia), and antifungal treatments received were recorded in the eCRF.

See Online for appendix

The local investigators were requested to classify patients as being colonised or infected with proven or putative IPA according to the AspICU classification being used at the time of the study, published by Blot and colleagues[10] (modified to patients with COVID-19, assuming no other systems were available at the time of the study). The criteria used by local investigators were given in the eCRF to standardise the case definition between centres. Standardised definitions are described in the appendix (pp 1–2).

Outcomes

The primary outcome was the prevalence of IFIs. Secondary outcomes were risk factors of proven or probable (pr/pb) CAPA, ICU mortality between the pr/pb CAPA and non-pr/pb CAPA groups, and associations of pr/pb CAPA and related variables with ICU mortality, identified by regression modelling. To evaluate pr/pb CAPA, the primary criteria evaluated were the most recent definitions from the European Confederation of Medical Mycology and International Society for Human and Animal Mycology (ECMM/ISHAM) published by Koehler and colleagues.[8] This classification is depicted in the appendix (pp 1–2); the final analysed populations of patients with and without pr/pb CAPA were based on the ECMM/ISHAM criteria. We also used the criteria for proven or putative IPA according to the AspICU algorithm (appendix pp 1–2).[10] Candidaemia was defined as one or more positive blood cultures for *Candida* spp. For patients with a positive qPCR for *P jirovecii*, the cycle threshold was recorded but it was not possible to discriminate between infection and colonisation because direct examination was not performed due to SARS-Cov-2-related hazards. The diagnosis of other IFIs was done on a case-by-case basis for respiratory or serum samples positive for other filamentous fungi. The full population for prevalence calculations and secondary analyses was defined as patients who did not oppose participation in the study, met the eligibility criteria, and were systematically screened for fungal respiratory microorganisms from study entry to discharge from the ICU with a minimum of three samples screened. The characteristics of patients with IFIs or pr/pb CAPA were compared to those without. Supplementary analyses of co-infections are ongoing and will be published at a later date.

Statistical analysis

Our objective was to enrol a minimum of 250 patients, thus allowing a precision of estimation (ie, 95% CI)

	All patients (n=509)*	Patients with IFI† (n=128)	Patients without IFI (n=381)	Univariate odds ratio (95% CI)	p value
Demographic characteristics*					
Sex at birth (n=509)					
Female	109 (21%)	24 (19%)	85 (22%)	..	..
Male	400 (79%)	104 (81%)	296 (78%)	1·24 (0·75–2·06)	0·40
Age, years (n=509)	59·4 (12·5)	62·0 (12·5)	58·5 (12·4)	1·02 (1·01–1·04)	0·0057
Weight, kg (n=491)	86·9 (17·6)	83·8 (17·3)	87·9 (17·6)	0·99 (0·97–1·00)	0·026
Height, cm (n=487)	172·4 (9·1)	171·5 (8·5)	172·7 (9·3)	0·99 (0·96–1·01)	0·22
Body-mass index, kg/m² (n=487)	29·3 (5·6)	28·4 (4·8)	29·6 (5·9)	0·96 (0·92–1·00)	0·042
Baseline characteristics*					
Dyslipidaemia (n=509)	21 (4%)	6 (5%)	15 (4%)	1·20 (0·46–3·16)	0·71
Diabetes (n=508)	167 (33%)	45 (35%)	122 (32%)	1·15 (0·75–1·75)	0·53
Hypertension (n=507)	254 (50%)	67 (53%)	187 (49%)	1·15 (0·77–1·72)	0·49
Chronic obstructive pulmonary disease (n=509)	34 (7%)	12 (9%)	22 (6%)	1·69 (0·81–3·52)	0·16
Asthma (n=509)	14 (3%)	6 (5%)	8 (2%)	2·29 (0·78–6·74)	0·13
Lymphopenia (n=503)	323 (64%)	82 (64%)	241 (63%)	1·02 (0·67–1·55)	0·92
Solid organ transplantation (n=509)	35 (7%)	15 (12%)	20 (5%)	2·40 (1·19–4·83)	0·015
Haematological malignancy (n=508)	6 (1%)	0	6 (2%)	0	0·98
Any immunosuppression (n=509)	55 (11%)	21 (16%)	34 (9%)	2·00 (1·12–3·60)	0·020
Treatments received for COVID-19*					
Lopinavir–ritonavir (n=509)	111 (22%)	23 (18%)	88 (23%)	0·73 (0·44–1·21)	0·23
Remdesivir (n=509)	20 (4%)	4 (3%)	16 (4%)	0·74 (0·24–2·24)	0·59
Oseltamivir (n=508)	40 (8%)	13 (10%)	27 (7%)	1·48 (0·74–2·96)	0·27
Cefotaxime (n=509)	25 (5%)	6 (5%)	19 (5%)	0·94 (0·37–2·40)	0·89
Spiramycin (n=509)	15 (3%)	5 (4%)	10 (3%)	1·51 (0·51–4·50)	0·46
Azithromycin (n=509)	10 (2%)	5 (4%)	5 (1%)	3·06 (0·87–10·74)	0·081
Hydroxychloroquine (n=508)	167 (33%)	35 (27%)	132 (35%)	0·71 (0·45–1·10)	0·12
Dexamethasone and anti-IL-6	29 (6%)	14 (11%)	15 (4%)	3·00 (1·40–6·40)	0·045
Dexamethasone (n=504)	202 (40%)	58 (46%)	144 (38%)	1·39 (0·92–2·08)	0·12
Anti-IL-6 (n=506)	38 (8%)	18 (14%)	20 (5%)	2·93 (1·50–5·73)	0·0017
Anti-IL-1 (n=508)	16 (3%)	4 (3%)	12 (3%)	0·99 (0·31–3·12)	0·99
Prone position (n=508)	394 (78%)	103 (80%)	291 (77%)	1·26 (0·77–2·07)	0·36
Clinical course data*					
Duration of mechanical ventilation, days (n=508)	27·1 (19·8)	31·2 (23·1)	25·8 (18·3)	1·01 (1·00–1·02)	0·0098
Simplified Acute Physiology Score II at admission (n=485)	44·1 (16·2)	47·6 (17·9)	42·9 (15·4)	1·02 (1·01–1·03)	0·0053
SOFA at admission (n=398)	7·4 (3·9)	7·8 (3·7)	7·3 (4·0)	1·03 (0·98–1·09)	0·25
SOFA at day 7 (n=366)	8·7 (4·2)	9·8 (3·9)	8·2 (4·3)	1·09 (1·04–1·16)	0·0014
SOFA at day 15 (n=261)	8·5 (4·6)	9·3 (4·3)	8·0 (4·7)	1·06 (1·00–1·12)	0·041
SOFA at discharge (n=285)	6·1 (6·0)	8·2 (6·2)	5·2 (5·7)	1·09 (1·04–1·13)	0·0001
Death in intensive care unit (n=509)	186 (37%)	71 (55%)	115 (30%)	2·88 (1·91–4·35)	<0·0001

Data are n (%) or mean (SD). IFI=invasive fungal infection. IL=interleukin. SOFA=Sequential Organ Failure Assessment. *Participants with data available are shown for each variable. †Patients with proven, probable, or possible IFI.

Table 1: **Demographic and baseline characteristics and clinical course data for the final analysis set**

between 6·3% and 13·7% with 80% power if the percentage of positive patients was 10%. Continuous variables are presented as means, with SDs, and categorical variables as numbers and percentages. Univariate logistic regression analysis was also performed for some variables (relevant baseline and demographic variables, treatments, and clinical course) to identify parameters associated with IFIs (pr/pb CAPA in particular) and ICU mortality. Multivariate analysis with Cox regression or logistic regression models, via a stepwise regression with a forward selection method, was used to identify the parameters most associated with IFIs, pr/pb CAPA, and mortality, adjusted for candidaemia for mortality regression. Receiver

	Prevalence or duration
Prevalence of infections	
CAPA*: pr/pb invasive aspergillosis	76 (15%)
pr/pb invasive fungal infection other than pr/pb CAPA (one or more)	38 (7%)
Candidemia	32 (6%)
Invasive mucormycosis	6 (1%)
Invasive fusariosis	1 (<1%)
Bacterial ventilator-associated pneumonia (n=509)†	374 (73%)
Cytomegalovirus infection (n=491)†	49 (10%)
Herpes simplex virus type 1 infection (n=491)†	76 (15%)
Duration of antifungal treatment, days	
Fluconazole (n=30)‡	19·2 (20·4)
Caspofungin (n=70)‡	7·9 (9·1)
Liposomal amphotericin B (n=34)‡	11·8 (27·5)
Voriconazole (n=73)‡	15·2 (16·1)
Isavuconazole (n=15)‡	12·3 (6·1)

Data are n (%) or mean (SD). CAPA=COVID-19-associated pulmonary aspergillosis. pr/pb=proven or probable. *CAPA status according to Koehler et al;[8] in addition, 24 (5%) of 509 patients with a compatible clinical context were positive for *Aspergillus* spp in non-bronchoalveolar lavage or bronchial or tracheal aspiration but did not meet the criteria for pr/pb CAPA; these were classified as possible IFIs. Some patients with pr/pb CAPA or possible CAPA also had other IFIs, thus 128 patients with pr/pb or possible IFIs had 138 episodes overall. †Number of patients with available data. ‡Number of patients receiving each treatment; denominator for each group (ie, patients with available data on antifungal treatments) was 162.

Table 2: **Prevalence of infections and antifungal treatments**

operating characteristic curves were used to confirm variable cutoffs (eg, for age). As CAPA prevalence was not collected at baseline, in multivariate Cox analysis, landmark analysis was also performed, in which landmark time was the mean of the delay of CAPA occurrence. Any treatments found to be significantly associated with pr/pb CAPA were analysed post-hoc in multivariate analyses for associations with other relevant factors. Survival curves were constructed with the Kaplan-Meier method and were compared via the log-rank test. Survival at ICU discharge was compared between the pr/pb CAPA and non-pr/pb CAPA groups, and, post hoc, between antifungal treatment and no treatment groups. Two-sided tests were used and considered statistically significant for p values less than 0·05. All statistical analyses were performed with SAS software (version 9.4). An independent data monitoring committee provided an external medical and statistical review of the data, in particular for verification of data entry and the management of missing data.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report, or in the decision to submit the paper for publication.

	pr/pb CAPA* (n=76)	Non-pr/pb CAPA* (n=433)	Univariate odds ratio (95% CI)	p value
Onset factors of CAPA*				
Sex at birth				
Female	14 (18%)	95 (22%)	..	..
Male	62 (82%)	338 (78%)	1·24 (0·67–2·32)	0·49
Age, years	76; 63·3 (12·5)	433; 58·7 (12·4)	1·03 (1·01–1·06)	0·0034
Weight, kg	73; 84·9 (19·0)	418; 87·3 (17·4)	0·99 (0·98–1·01)	0·28
Body-mass index, kg/m²	72; 28·7 (5·2)	415; 29·4 (5·7)	0·98 (0·93–1·02)	0·34
Dyslipidaemia	2 (3%)	19 (4%)	0·59 (0·13–2·58)	0·48
Diabetes	26 (34%)	141 (33%)	1·07 (0·64–1·80)	0·79
Hypertension	36 (47%)	218 (50%)	0·91 (0·55–1·48)	0·69
Chronic obstructive pulmonary disease	8 (11%)	26 (6%)	1·84 (0·81–4·24)	0·15
Asthma	5 (7%)	9 (2%)	3·32 (1·08–10·19)	0·036
Lymphopenia	56 (74%)	267 (63%)	1·68 (0·97–2·90)	0·064
Solid organ transplantation	8 (11%)	27 (6%)	1·77 (0·77–4·06)	0·18
Haematological malignancy	0	6 (1%)	0·00†	0·99
Any immunosuppression	11 (14%)	44 (10%)	1·50 (0·73–3·05)	0·27
Treatments received for COVID-19				
Lopinavir–ritonavir	20 (26%)	91 (21%)	1·34 (0·77–2·35)	0·30
Remdesivir	4 (5%)	16 (4%)	1·45 (0·47–4·46)	0·52
Oseltamivir	7 (9%)	33 (8%)	1·23 (0·52–2·88)	0·64
Cefotaxime	0	25 (6%)	0·00†	0·97
Spiramycin	2 (3%)	13 (3%)	0·87 (0·19–3·95)	0·86
Azithromycin	1 (1%)	9 (2%)	0·63 (0·08–5·03)	0·66
Hydroxychloroquine	18 (24%)	149 (34%)	0·59 (0·34–1·04)	0·065
Dexamethasone and anti-IL-6	8 (11%)	21 (5%)	2·31 (0·98–5·42)	0·055
Dexamethasone	34 (46%)	168 (39%)	1·33 (0·81–2·18)	0·27
Anti-IL-6	8 (11%)	30 (7%)	1·57 (0·69–3·57)	0·28
Anti-IL-1	3 (4%)	13 (3%)	1·32 (0·37–4·76)	0·67
Prone position	64 (84%)	330 (76%)	1·65 (0·86–3·17)	0·13
Clinical course data				
Duration of mechanical ventilation, days (n=508)‡	76; 31·8 (25·8)	432; 26·3 (18·4)	1·01 (1·00–1·02)	0·030
Simplified Acute Physiology II at admission (n=485)‡	74; 47·3 (17·4)	411; 43·5 (15·9)	1·01 (1·00–1·03)	0·060
SOFA at admission (n=398)‡	67; 7·8 (3·8)	331; 7·3 (4·0)	1·03 (0·96–1·10)	0·37
SOFA at day 7 (n=366)‡	61; 9·8 (3·8)	305; 8·5 (4·3)	1·07 (1·01–1·15)	0·032
SOFA at day 15 (n=261)‡	51; 9·8 (3·9)	210; 8·1 (4·7)	1·08 (1·01–1·16)	0·019
SOFA at discharge (n=285)‡	53; 9·2 (6·4)	232; 5·4 (5·7)	1·10 (1·05–1·16)	0·0001

Data are n (%), mean (SD), or n; mean (SD). pr/pb=proven or probable. CAPA= COVID-19-associated pulmonary aspergillosis. IL=interleukin. SOFA=Sequential Organ Failure Assessment. *CAPA status according to Koehler et al.[8] †Samples too small to calculate effect estimate and 95% CIs. ‡Number of patients with available data.

Table 3: **Demographic and baseline characteristics, immunosuppressive and antimicrobial therapies, and clinical course data between patients with and without pr/pb CAPA**

Results

Between Feb 29 and July 9, 2020, corresponding to the first wave of COVID-19, 576 mechanically ventilated patients with COVID-19 were screened and 565 were enrolled in the MYCOVID study, with 465 (82%) enrolments between March 15 and April 15, 2020. 509 patients were included in the final analysis, after 56 did not undergo complete mycological screening

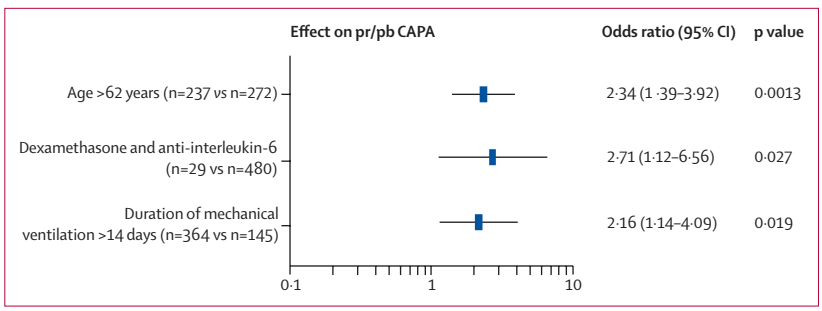

Figure 1: **Multivariate analysis of factors associated with pr/pb CAPA**
All significant variables in univariate analysis were included in the multivariate model, but only significant variables in the multivariate analysis are shown in the figure. CAPA=COVID-19-associated pulmonary aspergillosis. pr/pb=proven or probable.

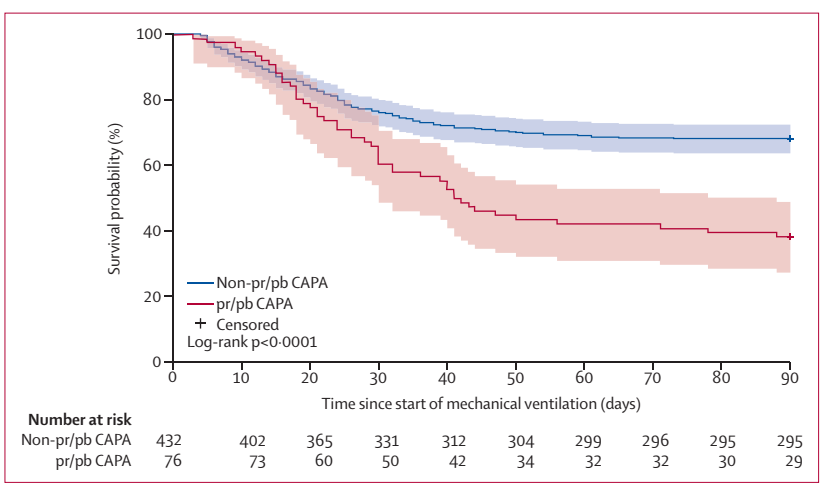

Figure 2: **Probability of survival according to pr/pb CAPA status**
Shading shows 95% CIs. No patients were censored. Data were missing for one patient in the non-pr/pb CAPA group. pr/pb=proven or probable. CAPA=COVID-19-associated pulmonary aspergillosis.

(<3 screening respiratory samples) and were excluded (appendix p 9). The mean number of samples (respiratory and serum) was 6·6 (SD 3·8) for the whole population. The number of included patients and the period of inclusion, according to the centre, are presented in the appendix (p 7).

The mean duration of stay in the ICU was 32·7 days (24·1). The baseline characteristics of the 509 patients included in the statistical analysis, and variables associated with IFIs, are shown in table 1. Mean age was 59·4 years (12·5) and 400 (79%) patients were men. Mean body-mass index was 29·3 kg/m² (5·6). Baseline characteristics and comorbidities were typical of COVID-19, with 167 (33%) patients (n=508 with available data) presenting with diabetes, 254 (50%; n=507) with hypertension, and 323 (64%; n=503) with lymphopenia according to local thresholds. The mean duration of mechanical ventilation was 27·1 days (19·8; n=508) and 186 (37%) of 509 patients died in the ICU. In total, 128 (25%) patients had 138 episodes of pr/pb or possible IFIs.

According to the ECMM/ISHAM CAPA definitions,[8] 76 (15%) of 509 patients fulfilled the criteria of pr/pb CAPA (appendix pp 1–2). According to the AspICU classification[10] that was available at the time of the study, 57 (11%) patients were classified by local investigators as having putative IPA and 48 (9%) as being colonised. In the cohort, 24 (5%) patients of 509 patients with a compatible clinical context of aspergillosis had samples that were positive for *Aspergillus* spp in non-bronchoscopic lavage, bronchial aspiration, or tracheal aspiration, but these episodes did not meet the criteria for pr/pb CAPA and were classified as possible IFI (non-pr/pb CAPA for the main analysis). 38 (7%) patients had other types of pr/pb IFI, sometimes with co-infections with one or two different fungi (n=10 patients), consisting of 32 (6%) cases of candidaemia, six (1%) of invasive mucormycosis, and one (<1%) of invasive fusariosis. Thurs, overall, we recorded 114 (22%) cases of pr/pb IFI (76 pr/pb CAPA and 38 other IFIs). Among the six patients with mucormycosis, three had fungal co-infection (two had CAPA and one candidaemia). Additionally, six patients had CAPA and candidaemia and one patient had CAPA, candidaemia, and fusariosis. Four patients had a positive PCR test for *Pneumocystis jirovecii* that could be classified either as infection or colonisation, although invasive status was undetermined. Aside from fungal infections, 374 (73%) patients were diagnosed with bacterial VAP, 76 (15%) with a HSV-1 viral infection, and 49 (10%) with a CMV infection (table 2). Overall, 162 (32%) patients received antifungal treatment during the mechanical ventilation period. Among them, 58 received more than one antifungal. Voriconazole and caspofungin were the two most frequently administered antifungal drugs (table 2). When comparing patients with pr/pb or possible CAPA to non-CAPA patients, the main significant differences among overall characteristics were the mean age and weight of patients, treatment with dexamethasone combined with anti-interleukin (IL)-6 or anti-IL-6 alone, duration of mechanical ventilation, SAPS II score at admission, and SOFA score at discharge in univariate analysis (appendix pp 3–4).

IPA according to modified AspICU criteria declared by the local investigators was diagnosed at a mean of 11·5 days (11·5) and a median of 8·0 days (IQR 4·0–14·0) after ICU admission. We used the case definition of ECMM/ISHAM CAPA according to Koehler and colleagues[8] in all subsequent analyses. We analysed the risk factors of pr/pb CAPA and effect of pr/pb CAPA on mortality. In univariate analysis, a main significant difference among overall characteristics between the group with pr/pb CAPA and the group without pr/pb CAPA was the mean age of patients (table 3). Other differences were the frequency of dexamethasone and anti-IL-6 administration (although marginally non-significant at p=0·055), the frequency of asthma, and clinical severity scores, with significantly higher SOFA scores for the pr/pb CAPA group than the non-pr/pb CAPA group at day 7, day 15, and discharge (table 3). According to multivariate analysis, three factors were independently associated with pr/pb CAPA: age older

than 62 years (odds ratio [OR] 2·34 [95% CI 1·39–3·92], p=0·0013), treatment with dexamethasone combined with anti-IL-6 (OR 2·71 [1·12–6·56], p=0·027), and a long duration of mechanical ventilation (>14 days; OR 2·16 [1·14–4·09], p=0·019; figure 1).

In univariate analysis, the mean duration of mechanical ventilation was significantly longer in patients with pr/pb CAPA at 31·8 days (25·8), versus 26·3 (18·4) for patients without pr/pb CAPA (table 3). At time of ICU discharge, survival curves showed that overall ICU mortality was significantly different between the two groups, at 32·1% (95% CI 27·7–36·7) for the non-pr/pb CAPA group versus 61·8% (50·0–72·8) for the pr/pb CAPA group (p<0·0001; figure 2). 58 (76%) of 76 patients with pr/pb CAPA received at least one antifungal drug, with 29 receiving more than one type. Among these patients, 44 (76%) received voriconazole, 20 (34%) received liposomal amphotericin B, 16 (28%) received caspofungin, 11 (19%) received isavuconazole, 30 (52%) received fluconazole, and five (9%) received other antifungal drugs (unspecified), alone or in combination.

SAPS II and SOFA scores showed significant associations with death in the ICU in univariate analysis (table 4). Additionally, three demographic characteristics were significantly associated with overall mortality in the ICU: increased age, immunosuppression, and, in particular, solid organ transplantation (table 4). Among the treatments and management measures administered in the ICU to the patient population, the lopinavir–ritonavir combination and anti-IL-1 were each associated with death in the ICU, whereas, cefotaxime and hydroxychloroquine were associated with survival, although these findings were based on small numbers (table 4). The duration of mechanical ventilation was longer for patients who survived (mean 28·9 days [21·2]) than for those who died (24·1 days [16·6]; table 4). Other treatment or management measures showed no significant associations with mortality in the ICU (table 4).

Among secondary infections, only fungal co-infections (pulmonary aspergillosis) were significantly associated with death. In addition to the survival curves showing mortality to be significantly increased for patients with pr/pb CAPA (figure 2), pr/pb CAPA was associated with death in the univariate analysis (table 4). Notably, a high mortality of 45·8% (95% CI 25·6–67·2) was also observed in the 24 patients with non-bronchoalveolar lavage or bronchial or tracheal aspiration positive for *Aspergillus* spp and a compatible clinical context of aspergillosis, compared with non-CAPA patients (appendix p 10). The detection of *Aspergillus* spp in respiratory samples by culture or qPCR was also associated with death (33 of 186 patients who died with positive culture samples *vs* 30 of 323 patients who survived, OR 2·11 [1·24–3·59], p=0·0060; and 37 of 186 patients who died with positive qPCR *vs* 43 of 323 patients who survived, OR 1·62 [1·00–2·62], p=0·0051, data not shown), regardless of aspergillosis status. The introduction of an anti-*Aspergillus* spp triazole (voriconazole, isavuconazole, or both drugs) did not modify mortality (appendix p 11), nor did other antifungal drugs improve survival (data not shown).

Aside from invasive *Aspergillus* infections, among the other fungal co-infections, only candidaemia was associated with mortality (table 4) by univariate analysis. We subsequently performed a multivariate analysis of factors associated with death, which identified three significant factors: age older than 62 years (HR 1·71 [95% CI 1·26–2·32], p=0·0005), solid organ transplantation (HR 2·46 [1·53–3·95], p=0·0002), and pr/pb CAPA (HR 1·45 [1·03–2·03], p=0·033; figure 3). Results for candidaemia were not significant. Results were similar with landmark analysis (mean landmark time 11 days) for age older than 62 years (HR 1·49 [95% CI 1·06–2·09], p=0·021), solid organ transplantation (HR 2·16 [95% CI 1·26–3·72], p=0·0054), and pr/pb CAPA (HR 1·78 [95% CI 1·24–2·57], p=0·0020).

	Death in the ICU (n=186)	Survival (n=323)	Univariate odds ratio (95% CI)	p value
Demographic characteristics				
Sex at birth				
Female	34 (18%)	75 (23%)	..	..
Male	152 (82%)	248 (77%)	1·35 (0·86–2·13)	0·19
Age, years	62·3 (10·9)	57·6 (13·1)	1·03 (1·02–1·05)	0·0001
Weight, kg	86·8 (17·8)	86·8 (17·5)	1·00 (0·99–1·01)	0·93
Body-mass index, kg/m²	29·2 (5·6)	29·3 (5·7)	0·99 (0·96–1·03)	0·73
Baseline characteristics				
Dyslipidaemia	8 (4%)	13 (4%)	1·07 (0·44–2·64)	0·88
Diabetes	61 (33%)	106 (33%)	1·01 (0·69–1·48)	0·97
Hypertension	101 (55%)	153 (47·5)	1·33 (0·92–1·91)	0·13
Chronic obstructive pulmonary disease	17 (9%)	17 (5%)	1·81 (0·90–3·64)	0·10
Asthma	8 (4%)	6 (2%)	2·37 (0·81–6·95)	0·11
Lymphopenia	127 (69%)	196 (62%)	1·36 (0·93–2·00)	0·11
Solid organ transplantation	22 (12%)	13 (4%)	3·20 (1·57–6·51)	0·0014
Haematological malignancy	3 (2%)	3 (1%)	1·76 (0·35–8·8)	0·49
Any immunosuppression	28 (15%)	27 (8%)	1·94 (1·11–3·41)	0·020
Treatments received for COVID-19				
Lopinavir–ritonavir	50 (27%)	61 (19%)	1·58 (1·03–2·42)	0·036
Remdesivir	7 (4%)	13 (4%)	0·93 (0·37–2·38)	0·88
Oseltamivir	20 (11%)	20 (6%)	1·82 (0·95–3·48)	0·070
Cefotaxime	1 (1%)	24 (7%)	0·07 (0·01–0·50)	0·0005
Spiramycin	5 (3%)	10 (3%)	0·86 (0·29–2·57)	0·79
Azithromycin	3 (2%)	7 (2%)	0·74 (0·19–2·90)	0·67
Hydroxychloroquine	51 (27%)	116 (36%)	0·67 (0·45–0·99)	0·047
Dexamethasone and anti-IL-6	15 (8%)	14 (4%)	1·94 (0·91–4·11)	0·085
Dexamethasone	84 (46%)	118 (37%)	1·44 (0·99–2·08)	0·053
Anti-IL-6	17 (9%)	21 (7%)	1·45 (0·74–2·82)	0·28
Anti-IL-1	10 (5%)	6 (2%)	2·99 (1·07–8·37)	0·037

(Table 4 continues on next page)

	Death in the ICU (n=186)	Survival (n=323)	Univariate odds ratio (95% CI)	p value
(Continued from previous page)				
Clinical course data				
Time in the ICU before mechanical ventilation (n=508)*	186; 0·1 (2·3)	322; −0·6 (5·6)	1·05 (0·99–1·11)	0·12
Duration of mechanical ventilation, days (n=508)*	186; 24·1 (16·6)	322; 28·9 (21·2)	0·99 (0·98–1·00)	0·011
Prone position (n=394)*	147 (79%)	247 (77%)	1·14 (0·74–1·77)	0·55
Simplified Acute Physiology Score II at admission (n=485)*	180; 46·8 (16·1)	305; 42·5 (16·1)	1·02 (1·01–1·03)	0·0043
SOFA at admission (n=398)*	142; 7·9 (3·9)	256; 7·2 (3·9)	1·05 (0·99–1·10)	0·080
SOFA at day 7 (n=366)*	128; 10·2 (4·1)	239; 7·9 (41)	1·14 (1·08–1·21)	0·0001
SOFA at day 15 (n=261)*	96; 10·7 (4·1)	165; 7·1 (4·4)	1·21 (1·13–1·29)	0·0001
SOFA at discharge (n=285)*	109; 12·6 (4·5)	176; 2·1 (2·1)	2·02 (1·70–2·39)	0·0001
pr/pb CAPA†	47 (25%)	29 (9%)	3·43 (2·07–5·68)	<0·0001
pr/pb invasive fungal infection other than pr/pb CAPA‡	21 (11%)	17 (5%)	2·29 (1·18–4·46)	0·015
Candidaemia	18 (10%)	14 (4%)	2·36 (1·15–4·87)	0·020
Bacterial ventilator-associated pneumonia	137 (74%)	237 (73%)	1·01 (0·67–1·53)	0·94
Cytomegalovirus infection (n=491)*	22/181 (12%)	27/310 (9%)	1·45 (0·80–2·63)	0·22
Herpes simplex virus 1 infection (n=491)*	30/181 (17%)	46/310 (15%)	1·14 (0·69–1·88)	0·61

Data are n (%), mean (SD), or n; mean (SD). ICU=intensive care unit. IL=interleukin. SOFA=Sequential Organ Failure Assessment. pr/pb=proven or probable. CAPA=COVID-19-associated pulmonary aspergillosis. *Number of patients with available data. †CAPA status according to Koehler et al.[8] ‡Numbers of cases of invasive mucormycosis and invasive fusariosis (table 2) were too low for analysis.

Table 4: **Patient characteristics, treatments, and secondary infections associated with death**

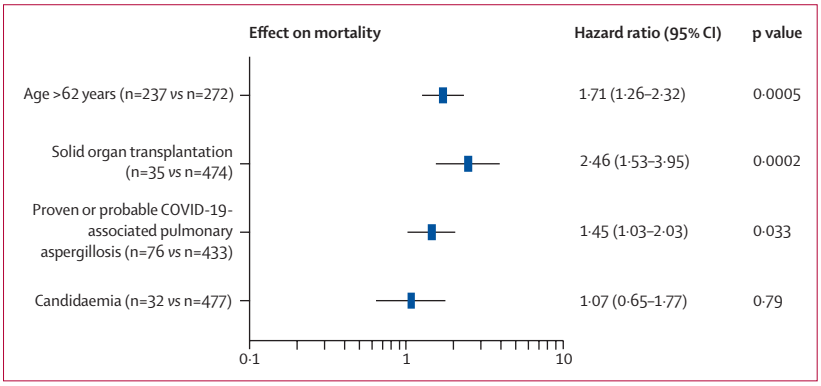

Figure 3: **Multivariate analysis of factors associated with death**
All significant variables in univariate analysis were included in the multivariate model; only significant variables in the multivariate analysis and variables of interest (candidaemia) are shown in the figure.

Multivariate analysis comparing patients with pr/pb CAPA to those without non-pr/pb CAPA revealed that treatment with dexamethasone and anti-IL-6 was independently associated with CAPA (figure 1). 29 patients received a combination of dexamethasone and anti-IL-6 for COVID-19. Among these patients, eight (28%) were in the pr/pb CAPA group versus 21 (72%) in the non-pr/pb CAPA group (table 5). The association of other factors with dexamethasone and anti-IL-6 treatment are summarised in table 5. pr/pb CAPA was significantly associated with dexamethasone and anti-IL-6 treatment in multivariate analysis (OR 2·54 [1·00–6·43], p=0·0049).

Discussion

To our knowledge, MYCOVID is the largest cohort study to date to investigate the prevalence of IFIs due to filamentous fungi and yeasts among mechanically ventilated ICU patients infected with SARS-CoV-2, with assessment of the associated mortality and risk factors for such secondary infections. Among the homogeneous population of 509 patients, we recorded 114 (22%) episodes of pr/pb IFI (76 pr/pb CAPA and 38 other IFIs), which increased to 138 episodes when including patients with non-bronchoalveolar lavage or bronchial or tracheal aspiration positive for *Aspergillus* spp and a compatible clinical context of aspergillosis. The high prevalence observed in this study might be related to several factors, such as the homogeneous population of patients with severe COVID-19 and ARDS, the rigorous monitoring dedicated to fungal diagnosis, the role of previous comorbidities, and the role of the treatment received. pr/pb CAPA was the most prevalent fungal infection in this cohort. Most published data have represented heterogeneous COVID-19 populations and mainly used the AspICU case definitions.[13,14] We used the recent ECMM/ISHAM CAPA definitions[8] and identified a high prevalence. Indeed, pr/pb CAPA was identified in 76 (15%) patients, which provides an update on previous estimates of CAPA prevalence among mechanically ventilated patients with COVID-19. Highly variable IPA prevalence estimates, ranging from 2% to 28%, have been reported in 10 other studies that each included more than 80 patients with severe COVID-19.[13–22] Such varying prevalence might be related to use of more or less stringent definitions of IPA and the monocentric nature of most of the studies, associated with variable local environmental risk and low numbers of patients (<150) included in eight of the studies.

We identified several factors associated with pr/pb CAPA by multivariate analysis. Patients with pr/pb CAPA were significantly older and had more severe disease based on SOFA score than patients without pr/pb CAPA. pr/pb CAPA was also associated with a longer duration of mechanical ventilation. Furthermore, patients with pr/pb CAPA more frequently received the combination therapy of dexamethasone and anti-IL-6, which was independently associated with pr/pb CAPA in multivariate analysis. Notably, patients treated with this combination were significantly younger than untreated patients and showed similar severity at admission, and had a similar duration of mechanical ventilation prior to the occurrence of CAPA (table 5).

We show, for the first time, that the combination of two immunomodulators (dexamethasone and anti-IL-6) is

associated with pr/pb CAPA, whereas the use of either dexamethasone or anti-IL-6 alone was not associated with pr/pb CAPA. However, as the number of patients receiving the dexamethasone and anti-IL-6 combination was low (n=29), further studies should be performed to confirm these results. Indeed, our study was done during the first wave of the COVID-19 pandemic at a time when these immunomodulators were not commonly used. Therapeutic management of severe COVID-19 pneumonia has evolved on the basis of results of clinical trials, and corticosteroids are now recommended and more frequently used. By contrast, the benefit–risk ratio of anti-IL-6 treatment needs to be carefully evaluated due to conflicting results concerning its use and clinical significance in patients with COVID-19.[23,24] Our results prompt us to warn clinicians about the use of this combination therapy and the risks associated with the resulting immunosuppression.

Other risk factors might be linked to environmental exposure but were not investigated in this study. Indeed, many centres have modified their existing air treatment to protect health-care workers from aerosolisation by creating negative air pressure zones, which could potentially increase the risk of *Aspergillus* exposure. Furthermore, some patients were treated in delocalised ICUs without any air treatment. Future studies should focus on the need to control environmental risk and use of early antifungal prophylaxis for high-risk patients receiving mechanical ventilation and immunosuppression.

Certain other respiratory viruses, such as influenza, also predispose patients to IPA.[1] In such patients, infection by respiratory viruses results in epithelial damage and disruption of normal ciliary clearance, aiding the invasion of pulmonary tissues by *Aspergillus*. Furthermore, NADPH-oxidase impairment is a recognised additional factor of pathogenicity during influenza infection. The prevalence of IPA in patients infected with SARS-CoV-2 appears to be similar to the known prevalence of IPA during severe seasonal influenza,[1] despite the accumulation of numerous facilitating factors in patients with COVID-19, including leukopenia or lymphopenia, T-cell perturbations, and treatment with corticosteroids, anti-IL-1, and anti-IL-6. Importantly, the median time of onset of IPA in patients with COVID-19 in the present study was 8·0 days (IQR 4·0–14·0) after ICU admission, corresponding to later coinfection than in influenza patients, in whom it generally occurs only 3 days after ICU admission.[1] These differences in time between ICU admission and onset of IPA might be due to differences in the pathophysiology of the two viral infections.[25]

A main finding of this study is the significantly higher mortality of patients with pr/pb CAPA, supported by both univariate and multivariate analyses, reaching 61·8% (50·0–72·8) by the time of ICU discharge in patients with pr/pb CAPA versus 32·1% (27·7–36·7) in patients without. In the group of patients with non-bronchoalveolar lavage positive for *Aspergillus* spp and a compatible clinical context of aspergillosis, a high mortality of 45·8% [95% CI 25·6–67·2] was also observed. Considering the debate around case definition, we observed a similar mortality outcome using the AspICU classification for putative IPA (31 [54%] deaths among 57 participants), even for patients categorised as colonised (17 [35%] deaths among 48 participants; data not shown). Although many authors have suggested that the presence of *Aspergillus* in

	Dexamethasone and anti-IL-6 treatment	No dexamethasone and anti-IL-6 treatment	Univariate OR (95% CI)	Multivariate OR (95% CI)
Age, years	29; 51·2 (13·3)	480; 59·8 (12·3)	0·95 (0·92–0·98)	0·29 (0·11–0·74)*
Hypertension	28	479	..	..
Yes	8 (29%)	246 (51%)	..	..
No	20 (71%)	233 (49%)	0·38 (0·16–0·88)	0·43 (0·19–1·01)†
Solid organ transplantation	29	480	..	..
Yes	4 (14%)	31 (6%)	..	..
No	25 (86%)	449 (94%)	2·32 (0·76–7·08)	..
Any immunosuppression	29	480	..	..
Yes	6 (21%)	49 (10%)	..	..
No	23 (79%)	431 (90%)	2·30 (0·89–5·91)	..
Duration of mechanical ventilation, days	29; 31·7 (19·3)	479; 26·9 (19·8)	1·01 (0·99–1·03)	..
Simplified Acute Physiology Score II at admission	25; 44·4 (15·2)	460; 44·1 (16·3)	1·00 (0·98–1·03)	..
Sequential Organ Failure Assessment at admission	25; 7·8 (3·6)	373; 7·4 (4·0)	1·03 (0·93–1·14)	..
Death in intensive care unit	29	480	..	..
Yes	15 (52%)	171 (36%)	..	..
No	14 (48%)	309 (64%)	1·94 (0·91–4·11)	..
Proven or probable CAPA‡	29	480	..	..
Yes	8 (28%)	68 (14%)	..	..
No	21 (72%)	412 (86%)	2·31 (0·98–5·42)	2·54 (1·00–6·43)§
Aspergillus spp in respiratory samples	29	480	..	..
Yes	9 (31%)	54 (11%)	..	..
No	20 (69%)	426 (89%)	3·55 (1·54–8·19)	..
pr/pb invasive fungal infection other than pr/pb CAPA	29	480	..	..
Yes	3 (10%)	35 (7%)	..	..
No	26 (90%)	445 (93%)	1·47 (0·42–5·09)	..
Candidaemia	29	480	..	..
Yes	3 (10%)	29 (6%)	..	..
No	26 (90%)	451 (94%)	1·79 (0·51–6·28)	..

Data are n, n (%), mean (SD), or n; mean (SD). All variables were analysed but only statistically significant variables or variables of interest are presented. IL=interleukin. OR=odds ratio. *p=0·0098. †p=0·054. ‡CAPA status according to Koehler et al.[8] §p=0·0049.

Table 5: **Univariate and multivariate analysis of factors associated with dexamethasone and anti-IL-6 combination treatment**

respiratory specimens from SARS-CoV-2-infected patients is a manifestation of colonisation, we advocate using the CAPA definitions and considering any marker indicating the presence of *Aspergillus* as an indication to perform a BAL, as also suggested by Van Grootveld and colleagues.[26] In the MYCOVID study, all positive pr/pb CAPA diagnoses obtained from respiratory or blood samples were significantly associated with increased mortality and should be considered to signal a possible diagnosis. Antifungal treatment with voriconazole or isavuconazole did not affect mortality in patients with pr/pb CAPA. However, a limitation of this study is that it was not designed to evaluate the efficacy of antifungal treatment. Nevertheless, the increased mortality in patients with pr/pb CAPA warrants consideration of early antifungal strategies, such as antifungal prophylaxis or a pre-emptive strategies for high-risk patients, including those receiving dexamethasone combined with anti-IL-6, as well as the implementation of air treatment measures. Another limitation of the study is that algorithms for COVID-19 treatment have changed substantially since the first wave and findings reported here might not be generalisable to further COVID-19 waves.

Aside from aspergillosis, the MYCOVID study highlights the high prevalence of other fungal infections, occurring in 38 (7%) of 509 patients, the most frequent being candidaemia in 32 (6%) patients. Several authors have noted a global increase in the incidence of candidaemia in patients with COVID-19, even candidaemia due to *Candida auris*, which is an emerging pathogen in health-care settings.[27,28] Among these reports, a recent review found an overall incidence of candidaemia in patients with COVID-19 ranging from 0·7% to 23·5%, of which most occurred in the ICU.[6] The reasons for such an increased incidence in this specific population are as yet poorly understood. Patients with COVID-19 are exposed to multiple risk factors for candidaemia, such as antibiotic therapy, corticosteroids, immunosuppressive therapy, and long ICU stays. Several studies have suggested that direct disruption of the intestinal barrier caused by COVID-19 might be an additional risk factor for candidaemia.[21,29] Indeed, enterocytes are infected by SARS-CoV-2, suggesting a possible link with *Candida* spp gut translocation.[30] A recent pilot study found enrichment of the faecal mycobiome with *Candida* and *Aspergillus* spp during the hospitalisation of 30 patients with COVID-19, compared with control patients with community-acquired pneumonia or healthy individuals.[31] However, further studies are required to establish whether such alterations can explain the observed increased incidence of candidaemia. The high number of deaths in patients with candidaemia in the MYCOVID study (18 [56%] deaths among 32 patients) warrants the analysis of risk factors and establishment of optimal management and prevention strategies for candidaemia in this context.

Contrary to aspergillosis and candidaemia, VAP and viral infections (CMV and HSV-1) were not associated with increased mortality in our study. However, although the diagnosis of VAP is well standardised, the same is not true for CMV and HSV-1 infections. Thus, excluding additional episodes of viral co-infections is not possible in our study and the data were based on individual reporting.

This study highlights the high prevalence and associated mortality of IPA and candidiasis in patients with ARDS-associated COVID-19. Antifungal drugs with high efficacy and low toxicity are available, along with non-invasive diagnostic tools, to allow the efficient management of IFIs. The high mortality associated with pr/pb CAPA indicates the importance of improving the management of this infectious complication. Overall, the present findings highlight the need for a high index of suspicion and the implementation of active surveillance. Further studies are required to establish whether early antifungal treatment or prophylaxis are needed if risk factors, such as those found in this study, are present.

Contributors

J-PG, ED, J-RZ, and M-EB conceived and designed the trial; accessed, verified, and oversaw analysis of the data; and wrote the manuscript. BL and JM contributed to the protocol design and statistical analysis of the data. All other authors contributed equally to the implementation of the study, inclusion of patients, and data collection. All authors had full access to all the data in the study and vouch for the accuracy and completeness of the data, data analyses, and interpretation and fidelity to the protocol. All authors critically reviewed and approved the final version and had final responsibility for the decision to submit for publication.

Data sharing

Data collected for the study, including deidentified individual participant data, a data dictionary defining each field in the set, and the statistical analysis plan will be made available to other researchers on request from the time of publication of this Article. Research proposals can be submitted to the corresponding authors (J-PG or M-EB).

Declaration of interests

J-PG reports personal fees from Gilead and grants and personal fees from Pfizer, outside of the submitted work. ED reports grants and non-financial support from Merck Sharp & Dohme and Gilead and non-financial support from Pfizer and Astellas, outside of the submitted work. AF reports personal fees and non-financial support from Merck Sharp & Dohme, grants from Janssen, personal fees and non-financial support from Gilead, and non-financial support from Pfizer, outside of the submitted work. C-EL reports personal fees from Carmat, Merck, BioMérieux, Brahms (part of Thermo Fisher Scientific), Bayer Healthcare, and Faron, outside of the submitted work. FraB reports grants from Astellas, personal fees from Merck Sharp & Dohme, and non-financial support from Pfizer, Merck Sharp & Dohme, and Astellas, outside of the submitted work. J-FT reports personal fees from Pfizer, Merck, Astellas, and Gilead, outside of the submitted work. FP reports non-financial support from Gilead and Pfizer, outside of the submitted work. EmC reports personal fees from Gilead, Baxter, and Sanofi-Genzyme, outside of the submitted work. AA reports personal fees from Pfizer and Gilead, outside of the submitted work. MC reports grants from Pfizer, outside of the submitted work. JuM reports non-financial support from Gilead, outside of the submitted work. SE reports grants, personal fees, and non-financial support from Aerogen and Fisher & Paykel, outside of the submitted work. GV reports grants and personal fees from BioMérieux and grants from SOS Oxygène and Janssen, outside of the submitted work. JeM reports grants from Pfizer and Gilead, outside of the submitted work. J-RZ reports grants and personal fees from Merck Sharp & Dohme and personal fees from Novartis and Pfizer, outside of

the submitted work. M-EB reports grants from Pfizer during the conduct of the study; grants and non-financial support from Gilead and Pfizer, and non-financial support from Merck Sharp & Dohme, outside of the submitted work. All other authors declare no competing interests.

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