

1 **High prevalence of fungal infections in mechanically ventilated COVID-19 patients in**
2 **the ICU: The French multicenter MYCOVID study**

3
4

5 Jean-Pierre Gangneux, Eric Dannaoui, Arnaud Fekkar, Charles-Edouard Luyt, Françoise
6 Botterel, Nicolas De Prost, Jean-Marc Tadié, Florian Reizine, Sandrine Houze, Jean-François
7 Timsit, Xavier Iriart, Béatrice Riu-Poulenc, Boualem Sendid, Saad Nseir, Florence Perlat,
8 Florent Wallet, Patrice Le Pape, Emmanuel Canet, Ana Novara, Melek Manai, Estelle
9 Perraud, Arnaud Thille, Sophie Brun, Yves Cohen, Alexandre Alanio, Bruno Mégarbane,
10 Muriel Cornet, Nicolas Terzi, Lionel Lamhaut, Estelle Sabourin, Guillaume Desoubeaux,
11 Stephan Ehrmann, Christophe Hennequin, Muriel Fartoukh, Gilles Nevez, Cécile Aubron,
12 Valérie Letcher-Bru, Ferhat Meziani, Julien Mayaux, Antoine Monsel, Marion Blaize,
13 Frédérique Boquel, Florence Robert-Gangneux, Yves Le Tulzo, Philippe Seguin, Hélène
14 Guegan, Brice Autier, Matthieu Lesouhaitier, Romain Pelletier, Sorya Belaz, Christine
15 Bonnal, Antoine Berry, Jordan Leroy, Nadine François, Chantal Fradin, Jean-Christophe
16 Richard, Sylvie Paulus, Laurent Argaud, Damien Dupont, Jean Menotti, Florent Morio,
17 Stéphane Gaudry, Carole Schwebel, Cécile Garnaud, Juliette Guitard, Solène Le Gal,
18 Dorothee Quinio, Jeff Morcet, Bruno Laviolle, Jean-Raph Zahar, Marie-Elisabeth Bougnoux

19
20

21 CHU de Rennes, Rennes (JP Gangneux, JM Tadié, F Reizine, F Robert-Gangneux, Y Le
22 Tulzo, P Seguin, H Guegan, B Autier, M Lesouhaitier, R Pelletier, S Belaz, J Morcet, B
23 Laviolle) ; CHU Hôpital Européen Georges Pompidou – APHP, Paris (E Dannaoui, A
24 Novara, M Manai) ; CHU La Pitié-Salpêtrière – APHP, Paris (A Fekkar, CE Luyt, J Mayaux,
25 A Monsel, M Blaize) ; CHU Henri Mondor – APHP, Créteil (F Botterel, N De Prost, F
26 Boquel) ; CHU Bichat – APHP, Paris (S Houze, JF Timsit, C Bonnal) ; CHU de Toulouse,
27 Toulouse (X Iriart, B Riu-Poulenc, A Berry, J Leroy, N François) ; CHU de Lille, Lille (B
28 Sendid, S Nseir, C Fradin) ; Hospices civils de Lyon, Lyon (F Persat, F Wallet, JC Richard, S
29 Paulus, L Argaud, D Dupont, J Menotti) ; CHU de Nantes, Nantes (P Le Pape, E Cannet, F
30 Morio) ; CHU de Poitiers, Poitiers (E Perraud, A Thille, S Gaudry) ; CHU Avicenne – APHP,
31 Bobigny (S Brun, Y Cohen, C Garnaud, JR Zahar) ; CHU Lariboisière/Saint-Louis – APHP,
32 Paris (B Megarbane, A Alanio) ; CHU de Grenoble, Grenoble (M Cornet, N Terzi, L
33 Lamhaut, C Schwebel, C Garnaud) ; CHU Necker Enfants malades – APHP, Paris (L
34 Lamhaut, E Sabourin, ME Bougnoux) ; CHU de Tours, Tours (G Desoubeaux, S Ehrmann, J
35 Guitard) ; CHU Saint-Antoine/Tenon – APHP, Paris (C Hennequin, M Fartoukh) ; CHU de
36 Brest, Brest (G Nevez, C Aubron, S Le Gal, D Quinio) ; CHU de Strasbourg, Strasbourg (V
37 Letcher-Bru, F Meziani) ; Institut Pasteur, Paris (ME Bougnoux).

38

39 *1 Covering letter*

40 *2 Manuscript including tables and panels*

41 *3 Figures*

42 *4 Authors statement form (see next section)*

43 *5 Declaration of interests and source of funding statements (see next section)*

44 *6 In-press papers—one copy of each with acceptance letters*

45 *7 Protocols and CONSORT details for randomised controlled trials (see Articles)*

46 *Texte: 3500 mots*

47 *30 réf*

48 **Summary** (300 mots)

49

50 **Background**

51 Patients with severe COVID-19 have clearly emerged as a population with a high risk of
52 invasive fungal infections (IFI). However, the prevalence of IFI has not yet been
53 prospectively assessed in large populations of mechanically ventilated COVID-19 patients.
54 We aimed to determine the prevalence of IFI, the risk factors, and the mortality associated
55 with COVID-19-associated pulmonary aspergillosis (CAPA) in mechanically ventilated
56 patients in the ICU.

57 **Methods**

58 We performed a national multicenter observational cohort study among 18 French ICUs and
59 enrolled 576 mechanically ventilated COVID-19 patients. Patients were systematically
60 screened for fungal microorganisms once/twice a week during the period of mechanical
61 ventilation up to ICU discharge, and CAPA was defined according to recent definitions. The
62 trial is registered at ClinicalTrials.gov, NCT04368221.

63

64 **Findings**

65 In total, 509 patients with ≥ 3 screening samples were analyzed (mean age of 59.4 years and
66 78.6% were male). The prevalence of proven/probable CAPA was 17.1% (87/509) and 4.7%
67 (24/509) for possible CAPA. Thirty-eight (7.5%) patients experienced other IFIs: 32
68 candidemia (6.3%), six mucormycosis (1.2%), and one fusariosis. Four patients had a positive
69 PCR for *Pneumocystis jirovecii*. Multivariate analysis of factors associated with death in the
70 entire study population showed three significant factors: age ≥ 62 (HR: 1.83 [95% CI 1.35-
71 2.48]), solid organ transplantation (2.33 [1.43-3.79]), and proven/probable CAPA (1.77
72 [1.25-2.48]). Severity scores were significantly higher for CAPA and mortality was
73 significantly higher in cases of proven/probable and possible CAPA than no CAPA: 59.8%,
74 45.8%, and 30.9%, respectively ($p < 0.0001$). Anti-IL6-treated patients were characterized by
75 a significantly younger age, dexamethasone treatment (6.64 [2.89-15.23]), positive
76 galactomannan antigenemia (5.01 [1.47-17.09]), and proven/probable/possible CAPA (2.60
77 [1.11-6.06]).

78 **Interpretation**

79 This study shows the dramatic prevalence of CAPA and candidiasis associated with a high
80 mortality rate in mechanically ventilated COVID-19 patients. These findings highlight the
81 need of active surveillance for fungal pathogens in severe COVID-19 patients.

82

83 **Funding**

84 Pfizer Inc., NY, USA

85

86

87 **Key words:** Covid-19 associated pulmonary aspergillosis (CAPA), invasive pulmonary
88 aspergillosis (IPA) Acute respiratory distress syndrome (ARDS), mechanical ventilation,
89 ICU, Candidemia, anti-IL6

90

91

92 **Research in context a faire**

93 *Autres Recos:*

94 *We use a comma before the final “and” or “or” in a list of items • Type decimal points midline (ie, 23.4, not*
95 *23.4). To create a midline decimal on a PC: hold down ALT key a*

96 *Figures : no less than 300 dpi when set at its final printed size. Ideal file formats are TIF or JPG*

98 **Introduction**

99 Fungal infections are known to be among the infectious complications related to the damage
100 caused by viral pulmonary infections, particularly in intensive care unit (ICU) patients with
101 severe acute respiratory distress syndrome (ARDS). Indeed, invasive pulmonary aspergillosis
102 (IPA) is now a well-known complication of the clinical course of critically ill patients with
103 influenza.^{1, 2} Patients with severe COVID-19 have also emerged as a population with a high
104 risk of fungal infections.^{3, 4} COVID-19 is associated with epithelial lung damage,
105 lymphopenia, dysfunction of the cell response, and the use of broad spectrum antibiotics,
106 dexamethasone, and immunosuppressive therapies.⁵ Thus, adherence of *Aspergillus* conidia
107 may be promoted by prior damage of the lungs due to SARS- CoV-2 infection and multiple
108 risk factors may lead to tissue invasion after conidia germination.^{6, 7}

109 During the COVID-19 pandemic, several case series have been published that suggest an
110 increased risk of IPA in patients with severe COVID-19 (COVID-19-associated pulmonary
111 aspergillosis - CAPA), with an estimated prevalence of <5% to >30%, whereas the prevalence
112 of candidemia and other fungal infections is still poorly known.⁵ However, the heterogeneity
113 of monitoring protocols, diagnostic tools, and severity of COVID-19 patients included in
114 various studies (all hospitalized COVID-19 patients, only patients in the ICU, or only patients
115 in the ICU with ARDS) make it difficult to interpret the data published in the literature.

116 It is only recently that specific criteria for the case definition and diagnosis of CAPA were
117 published in The Lancet Infectious Diseases journal.⁸ Consensual recommendations are
118 essential because patients who have been infected during the pandemic do not meet the usual
119 EORTC/MSG criteria for invasive aspergillosis, as there are no host-related risk factors nor
120 specific clinical features.⁹ In addition, the more focused AspICU algorithm to diagnose
121 invasive pulmonary aspergillosis (IPA) in critically ill patients does not include new
122 diagnostic developments and appears to be ill adapted to COVID-19 patients.^{10, 11}
123 Furthermore, the typical radiological features of aspergillosis may be difficult to assess in
124 ARDS-associated COVID-19.¹² Finally, the sensitivity and specificity of current mycological
125 tests have still not been completely evaluated in this specific population.

126 Here, we sought to characterize the prevalence, risk factors, and outcome of invasive fungal
127 infections (IFI), including CAPA and candidemia, in COVID-19 infected and mechanically
128 ventilated patients in the ICU using the new definitions of CAPA and a standardized and
129 rigorous protocol registered at ClinicalTrials.gov ID: NCT04368221.

130

131 **Methods**

132 **Study design and participants**

133 We performed a national multicenter observational cohort study among ICU COVID-19
134 patients to determine the burden of IFI. Adult patients (≥ 18 years) were eligible for enrolment
135 if they had an RT-PCR-confirmed diagnosis of SARS-CoV-2 infection and required
136 mechanical ventilation for ARDS. Patients were consecutively included between February
137 and July 2020 in 18 participating university hospital ICUs across France (**figure S1**). The
138 patients' clinical and biological data were collected as part of their follow-up from admission
139 to discharge from the ICU. Data were collected anonymously and managed using eCRF
140 available at ClinicalTrials.gov ID: NCT04368221.

141 The MYCOVID study was conducted in full concordance with the principles of the
142 Declaration of Helsinki and the laws, and regulations of France. This study was approved by
143 the French authorities (Comité Consultatif sur le Traitement de l'information en matière de
144 Recherche dans le domaine de la Santé, and Commission Nationale de L'Informatique et des
145 Libertés) and registered as No. 910346. According to French policy, a non-opposition
146 statement was obtained for all included patients or, where applicable, a relative or their legal
147 representative, signifying that all received written detailed information about the objectives of
148 the study and were free to request withdrawal of their data at any time. The study protocol
149 was reviewed and approved by the ethics committee of Rennes University Hospital, Rennes,
150 France (Approval no. 20.56). The study was registered at clinicaltrial.gov under the number
151 NCT04368221.

152

153 **Procedures**

154 In each participating ICU, patients with ARDS-associated COVID-19 who were mechanically
155 ventilated were systematically screened for fungal respiratory microorganisms once or twice a
156 week during the period of mechanical ventilation up to ICU discharge, resulting in a
157 minimum of three samples if discharge occurred after 15 days (**figure 1A**). Respiratory
158 samples included tracheal aspiration (TA), and/or bronchial aspiration (BA), and/or
159 bronchioloalveolar lavage (BAL). The local microbiological laboratory in each participating
160 center processed the fungal cultures of the samples. Real-time quantitative PCR (RT-qPCR)
161 for *Aspergillus*, *Pneumocystis jirovecii*, and Mucorales were also performed on the same
162 samples either locally or following referral to a specialized laboratory. The other

163 microbiology samples and tests were performed according to the local ICU hospital standard
164 of care. Specific blood biomarkers (qPCR for either *Aspergillus* or Mucorales and
165 galactomannan antigenemia) were sought if respiratory samples were positive either for
166 filamentous fungi or *P. jirovecii*. Demographic and clinical data (underlying diseases, gravity
167 scores (Simplified Acute Physiology Score II [SAPS II], Sequential Organ Failure
168 Assessment [SOFA], anti-COVID-19 treatments), laboratory data (lymphopenia, viral
169 detection of HSV and CMV, bacterial and fungal ventilated-associated pneumonia [VAP],
170 and candidemia), and antifungal treatments received were recorded in the eCRF.

171 The local investigators were requested to classify patients as being colonized or infected with
172 proven or putative pulmonary aspergillosis according to the AspICU classification currently
173 being used at the time of the study. During the analysis of data, the CAPA consensual
174 definitions were published by Koehler et al. and were thus also used for the statistical
175 analysis.

176

177 **Outcomes**

178 The outcomes of interest were the prevalence of IFIs and fungal respiratory colonization and
179 their impact on ICU mortality. CAPA was defined and classified according to the most recent
180 definitions.⁸ The characteristics of CAPA patients were compared to those of non-CAPA
181 patients and to proven/putative IPA according to the AspICU algorithm. Candidemia was
182 defined as one or more positive blood cultures for *Candida* spp. For patients with a positive
183 qPCR for *P. jirovecii*, the Ct was recorded but it was not possible to discriminate between
184 infection and colonization. Invasive mucormycosis were defined by the local investigators
185 according to the clinical signs associated to a positive specific qPCR or culture from
186 respiratory samples and/or a positive blood qPCR for the same genus. The diagnosis of other
187 invasive fungal infections was performed on a case-by-case basis for respiratory samples with
188 positive cultures for other filamentous fungi.

189

190 **Statistical analysis**

191 An independent data monitoring committee provided an external medical and statistical
192 review of the efficacy and safety data. Continuous variables are presented as means, with
193 standard deviations, and medians (interquartile range) and categorical variables as numbers
194 (percentage), with the corresponding 95% confidence interval. Subgroups (for example,
195 positive and negative patients) were compared using standard statistical approaches: chi² tests
196 for categorical variables and Student t or Wilcoxon rank sum tests for continuous variables.

197 Multivariate analysis using a Cox model or logistic regression was performed to determine the
198 parameters most highly associated with invasive fungal infections and mortality. Survival
199 curves were constructed using the Kaplan-Meier method and were compared using the log
200 rank test. Two-sided tests were performed and considered statistically significant for p-values
201 <0.05 . All statistical analyses were performed using SAS 9.4 software (SAS Institute, Cary,
202 NC, USA). The full population for prevalence calculations was defined as patients who did
203 not oppose participation in the study, met the eligibility criteria, and were systematically
204 screened for fungal respiratory microorganisms once or twice a week from entry to discharge
205 from the ICU.

206

207 **Role of the funding source**

208 The study sponsor (Pfizer Inc., NY, USA) was not involved in the study design, collection,
209 analysis, or interpretation of the data, writing of the report, or the decision to submit the paper
210 for publication. The corresponding author had full access to all the data and the final
211 responsibility to submit the manuscript for publication. All authors vouch for the accuracy
212 and completeness of the data, data analyses, and interpretation and fidelity to the protocol and
213 approved the final manuscript for submission.

214

215 **Results**

216 Between February 29 and July 9, 2020, 576 mechanically ventilated COVID-19 patients, from
217 18 French ICUs, were enrolled in the MYCOVID study. The final analysis was carried out on
218 509 patients, as 11 were withdrawn/excluded and 56 did not undergo complete mycological
219 screening or follow-up (<3 screening samples) (figure 1B). The mean number of samples
220 (respiratory and serum) was 6.6 ± 3.8 (median 6.0 [95% CI 6.3-7.0]) for the whole population.
221 The number of included patients and the period of inclusion according to the center are
222 presented in figure S1.

223

224

225 *Baseline characteristics*

226 The mean duration of ICU stay was 32.7±24.1 days (median 26.0, minimum 1, maximum
 227 204). The baseline characteristics of the 509 patients included in the statistical analysis are
 228 shown in **table 1**. The mean age was 59.4±12.5 years (median 60.7) and 79% were male. The
 229 mean body mass index was 29.3±5.6 (median 28.4 [95% CI 28.7-29.8]). The baseline
 230 characteristics and comorbidities were typical of COVID-19, with 32.9% (28.8-37.1) of
 231 patients presenting with diabetes mellitus, 50.1% (45.7-54.5) with high blood pressure, and
 232 64.2% (59.9-68.4) with initial lymphopenia. Anti-COVID-19 treatments are listed in **table 1**.
 233 The mean duration of mechanical ventilation was 27.1±19.8 days (25.5-28.9). Severity
 234 scores (SAPS II and SOFA) are presented in **table 1** and 186/509 patients died in the ICU
 235 (36.5% [32.3-40.9]).

236

237

238 **Table 1. Demographic and baseline characteristics and clinical course data for 509**
 239 **mechanically ventilated COVID-19 patients in the intensive care unit (ICU).**

240

	Demographic characteristics
	Mean ± SD, and 95% CI
Sex at birth (509)	
- Female	109 (21.4% [17.9 - 25.2])
- Male	400 (78.6% [74.8 - 82.1])
Age, years (509)	59.4 ± 12.5 (58.1 - 60.4)
Weight, kg (490)	86.9 ± 17.6 (85.3 - 88.5)
Height, cm (490)	172.4 ± 9.1 (171.6 - 173.2)
BMI, kg/m ² (490)	29.3 ± 5.6 (28.8 - 29.8)
	Baseline characteristics
	n (% , [95% CI])
Obesity	62 (12.2% [9.5 - 15.3])
Dyslipidemia	21 (4.1% [2.6 - 6.2])
Diabetes mellitus	167 (32.9% [28.8 - 37.1])
High blood pressure	254 (50.1% [45.7 - 54.5])
COPD	34 (6.7% [4.7 - 9.2])
Asthma	14 (2.8% [1.5 - 4.6])
Initial lymphopenia	323 (64.2% [59.9 - 68.4])
Transplantation	35 (6.9% [4.8 - 9.4])
Hematological malignancy	6 (1.2% [0.4 - 2.6])
All immunosuppression	55 (10.8% [8.2 - 13.8])
Lopinavir+Ritonavir (Kaletra)	111 (21.8% [20.7 - 33.9])
Remdisivir	20 (3.9% [2.4 - 6.0])
Oseltamivir	40 (7.9% [5.7 - 10.6])

Cefotaxime	25 (4.9% [3.2 - 7.2])
Rovamycin	15 (2.9% [1.7 - 4.8])
Azithromycin	10 (2.0% [0.9 - 3.6])
Hydroxychloroquine	167 (32.9% [28.8 - 37.1])
Dexamethasone	202 (40.1% [35.8 - 44.5])
Anti-IL6	38 (7.5% [5.4 - 10.2])
Anti-IL1	16 (3.1% [1.8 - 5.1])
Prone position	394 (77.6% [73.7 - 81.1])
Clinical course data	
Mean \pm SD, and 95% CI	
Duration of mechanical ventilation, days (508)	27.1 \pm 19.8 (25.4 - 28.9)
SAPS II – admission (485)	44.1 \pm 16.2 (42.6 - 45.5)
SOFA – admission (398)	7.4 \pm 3.9 (7.0 - 7.8)
SOFA – day 7 (367)	8.7 \pm 4.2 (8.3 - 9.1)
SOFA – day 15 (261)	8.5 \pm 4.6 (7.9 - 9.0)
SOFA - discharge (285)	6.1 \pm 6.0 (5.4 - 6.8)
Death in ICU (509)	186 (36.5% [32.3 - 40.9])

241 BMI: body-mass index, COPD: chronic obstructive pulmonary disease, SAPS II: Simplified Acute Physiology
242 Score II; SOFA: Sequential Organ Failure Assessment.

243

244 *Prevalence of secondary infections*

245 The prevalence of secondary infections is presented in [table 2](#). We compared the observed
246 prevalence of invasive aspergillosis using either the definition according to Koehler et al.⁸
247 (i.e. proven/probable/possible CAPA) or that according to Blot et al.¹¹ (i.e. proven/putative
248 IPA). In total, 111/509 (21.8%) patients were classified as having CAPA according to
249 Koehler et al.;⁸ 87/509 (17.1%) fulfilled the criteria for proven/probable CAPA and 24/509
250 (4.7%) for possible CAPA. Use the AspICU classification published by Blot et al.¹¹ resulted
251 in 57/509 (11.2%) patients being classified by the local investigators as proven/putative IPA
252 and 50/509 (9.8%) as colonized. Concerning other IFIs, 38 patients (7.5%) experienced
253 another invasive fungal infection, sometimes with co-infections with one or two different
254 fungi, consisting of 32 cases of candidemia (6.3%), six of invasive mucormycosis (1.2%),
255 and one of invasive fusariosis. Of note, four patients had a positive PCR for *Pneumocystis*
256 *jirovecii* that could be classified either as infection or colonization. Aside from fungal
257 infections, 374 (73.5%) patients were diagnosed with bacterial ventilator-associated
258 pneumonia (VAP), 76 (15.5%) with a HSV1 viral infection, and 49 (10.0%) with a CMV
259 infection ([table 2](#)). Overall, 162 (31.8%) patients received antifungal treatment during the

260 mechanical ventilation period, among them 58/162 received more than one antifungal).
 261 Voriconazole and caspofungin were the two most frequently administered antifungal drugs
 262 (table 2).

263
 264

265 **Table 2. Prevalence of infections in 509 mechanically ventilated COVID-19 patients in**
 266 **the intensive care unit (ICU) and antifungal treatments.**

	Prevalence of infections n (%), [95% CI]	267 268 269	*CA PA acco rdin g to Koe hler et al. ⁸ , pr/p b: prov en/p roba ble, pos: poss ible
CAPA status*			
- pr/pb invasive aspergillosis	87 (17.1% [13.9 - 20.6])		
- pos invasive aspergillosis	24 (4.7% [3.0 - 6.9])		
AspICU status#		273	
- pr/pu invasive aspergillosis	57 (11.2% [8.6 - 14.3])	274	
- Aspergillus colonization	50 (9.8% [7.4 - 12.7])	275	
Other invasive fungal infections (one or more)	38 (7.5% [5.3 - 10.1])	276	
- Candidemia	32 (6.3% [4.3 - 8.8])		
- Invasive mucormycosis	6 (1.2% [0.4 - 2.5])		
- Invasive fusariosis	1 (0.2% [0.0 - 1.1])		
Bacterial VAP	374 (73.5% [69.4 - 77.3])		
CMV infection	49 (10.0% [7.5 - 13.0])	283	
HSV1 infection	76 (15.5% [12.4 - 19.0])	284	
	Duration of antifungal treatment (days)		#Ac cord ing to Blot et al. ¹¹ , pr/p u:
	Mean ± SD (min, median, max)		
Fluconazole (n=30)	19.2 ± 20.4 (2, 14, 84)		
Caspofungin (n=70)	7.9 ± 9.1 (1, 5, 60)		
Liposomal amphotericin B (n=34)	11.8 ± 27.5 (1, 4, 156)		
Voriconazole (n=73)	15.2 ± 16.1 (1, 10, 88)		
Isavuconazole (n=15)	12.3 ± 6.1 (3, 12, 26)		
		294	

295 proven/putative

296

297

298 *Invasive aspergillosis*

299 We used the case definition of CAPA according to Koehler et al.⁸ in all subsequent analyses.
 300 Invasive aspergillosis was the most prevalent IFI in this cohort. We analyzed the risk factors
 301 and impact of CAPA on mortality. The main significant differences between the
 302 proven/probable/possible CAPA group and the non-CAPA group were the mean age of the
 303 patients (62.2±13.3 versus 58.6±12.2, respectively, $p=0.007$) and an immunosuppressed
 304 status (16.2% versus 9.3%, respectively, $p=0.038$), particularly transplantation (11.7% versus
 305 5.5%, respectively, $p=0.023$) (table 3). Comparison of the proven/probable CAPA group with
 306 others (including possible CAPA and non-CAPA) showed significant differences for exactly
 307 the same variables: higher mean age ($p=0.025$), total immunosuppression ($p=0.034$), and
 308 transplantation ($p=0.05$). Thirty-eight patients received anti-IL6 treatment for COVID-19,

309 showing a statistical difference between the CAPA group (15.3%) and non-CAPA group
 310 (5.3%, $p=0.0016$).

311 The mean duration of mechanical ventilation was 31.3 ± 24.5 days for patients with CAPA
 312 (32.1 ± 25.3 days for proven/probable CAPA and 28.1 ± 21.7 for possible CAPA) versus
 313 26.0 ± 18.1 for patients without CAPA ($p=0.013$). The severity scores were significantly
 314 higher for the CAPA patients (table 3). Survival curves show that mortality was significantly
 315 different between the three groups: 30.9%, 45.8%, and 59.8% for the non-CAPA, possible
 316 CAPA, and proven/probable CAPA groups, respectively ($p<0.0001$) (figure 2). Seventy-
 317 seven percent (67/87) of proven/probable CAPA patients received at least one antifungal
 318 agent (33/67 received more than one antifungal). Among them, 67.2% (45/67) received
 319 voriconazole, 31.3% (21/67) liposomal amphotericin B, 29.9% (20/67) caspofungin, 16.4%
 320 (11/67) isavuconazole, and 16.4% (11/67) other antifungal drugs, alone or in combination.

321

322

323

324 **Table 3. Demographic and baseline characteristics, immunosuppressive and**
 325 **antimicrobial agents, and severity scores between CAPA and non-CAPA patients under**
 326 **mechanical ventilation.**
 327

	pr/pb/pos CAPA* (n=111)	Non-CAPA* (n=398)	
Onset factors of CAPA* (n, %)	n, value or % (95% CI)	n, value or % (95% CI)	p
Sex at birth			0.84
Female (109, 21%)	23, 20.7% (13.6-29.5)	86, 21.6% (17.7-26.0)	
Male (400, 79%)	88, 79.3% (70.5-86.4)	312, 78.4% (74.0-82.3)	
Age, years	111	398	0.005
Mean \pm SD, (95% CI)	62.2 ± 13.3 (59.7-64.7)	58.6 ± 12.2 (57.4-59.8)	
Weight, kg	104	387	0.07
Mean \pm SD, (95% CI)	84.1 ± 18.5 (80.5-87.7)	87.3 ± 17.3 (85.9-89.4)	
BMI, kg/m ²	102	384	0.11
Mean \pm SD, (95% CI)	28.5 ± 5.4 (27.4-29.6)	29.5 ± 5.7 (28.9-30.1)	
Obesity (62, 12.2%)	9 8.1% (3.8-14.8)	53 13.3% (10.1-17.1)	0.14
Diabetes mellitus (167, 32.9%)	41 36.9% (28.0-46.6)	126 31.7% (27.2-36.6)	0.31
High blood pressure (254, 50.1%)	57 51.8% (42.1-61.4)	197 49.6% (44.6-54.7)	0.68
COPD (34, 6.7%)	11 9.9% (5.1-17.0)	23 5.8% (3.7-8.5)	0.12
Asthma (14, 2.8%)	5 4.5% (1.5-10.2)	9 2.3% (1.0-4.2)	0.20
Transplantation (35, 6.9%)	13 11.7% (6.4-19.2)	22 5.5% (3.5-8.2)	0.023
Hematological malignancy	0	6	0.35

(6, 1.2%)	0.0% (0.0-3.3)	1.5% (0.6-3.3)	
All immunosuppression (55, 10.8%)	18 16.2% (9.9-24.4)	37 9.3% (6.6-12.6)	0.038
Lopinavir+Ritonavir (Kaletra) (111, 21.8%)	21 18.9% (12.1-27.5)	90 22.6% (18.6-27.0)	0.40
Remdisivir (20, 3.9%)	4 3.6% (1.0-9.0)	16 4.0% (2.3-6.4)	1.0
Oseltamivir (40, 7.9%)	11 9.9% (5.1-17.0)	29 7.3% (4.9-10.3)	0.42
Cefotaxime (25, 4.9%)	5 4.5% (1.5-10.2)	20 5.0% (3.1-7.7)	0.82
Rovamycin (15, 2.9%)	6 5.4% (2.0-11.4)	9 2.3% (1.0-4.2)	0.11
Azithromycin (10, 2.0%)	4 3.6% (1.0-9.0)	6 1.5% (0.6-3.3)	0.24
Hydroxychloroquine (167, 32.9%)	30 27.0% (19.0-36.3)	137 34.5% (29.8-39.4)	0.17
Dexamethasone (202, 40.1%)	48 44.0% (34.5-53.9)	154 39.0% (34.1-44.0)	0.34
Anti-IL6 (38, 7.5%)	17 15.3% (9.2-23.4)	21 5.3% (3.3-8.0)	0.0016
Anti-IL1 (16, 3.1%)	3 2.7% (0.6-7.7)	13 3.3% (1.8-5.5)	1.0
Duration of mechanical ventilation (508)	111 31.3 ± 24.5 (26.6-35.9)	397 26.0 ± 18.1 (24.2-27.8)	0.013
Prone position (394, 77.6%)	89 80.2% (71.5-87.1)	305 76.8 (72.4%-80.9)	0.52
SAPS II – admission (485, 44.1 ± 16.2)	107 47.3 ± 17.5 (43.9-50.6)	378 43.2 ± 15.7 (41.6-44.8)	0.021
SOFA – admission (398, 7.4 ± 3.9)	100 7.8 ± 3.7 (7.1-8.6)	298 7.3 ± 4.0 (6.8-7.7)	0.22
SOFA – day 7 (367, 8.7 ± 4.2)	93 9.6 ± 3.7 (8.8-10.4)	273 8.4 ± 4.4 (7.9-8.9)	0.010
SOFA – day 15 (261, 8.5 ± 4.6)	78 9.2 ± 4.2 (8.3-10.2)	183 8.1 ± 4.8 (7.4-8.8)	0.075
SOFA - discharge (285, 6.1 ± 6.0)	81 8.3 ± 6.1 (7.0-9.7)	204 5.3 ± 5.8 (4.5-6.1)	<0.0001

328 *According to Koehler et al.⁸. SAPS II: Simplified Acute Physiology II, SOFA: Sequential Organ Failure
329 Assessment, BMI: body-mass index, COPD: chronic obstructive pulmonary disease.
330

331
332
333
334
335
336
337
338
339
340
341
342
343
344
345
346
347
348
349
350
351
352
353
354
355
356
357
358
359
360
361
362
363

Mortality

The severity of the SAPS II and SOFA scores was significantly associated with death in the ICU: 186/509 patients (36.5% [95% CI 32.3-40.9], [table 4](#)).

Three host factors were significantly associated with overall mortality in the ICU: older age ($p=0.0001$), immunosuppression ($p=0.019$), and, in particular, transplantation ($p=0.0008$, [table 4](#)). Among the treatments and management measures administered in the ICU to the patient population, the combination of lopinavir+ritonavir (Kaletra) ($p=0.035$) and anti-IL1 ($p=0.036$) were associated with death in the ICU, whereas cefotaxime was associated with survival ($p=0.0005$, [table 4](#)). The duration of mechanical ventilation was longer for survivors (28.9 ± 21.2 [95% CI 26.5-31.2]) than for the patients who died (24.1 ± 16.6 [21.7-26.5], [table 4](#)). Other treatment or management measures showed no significant statistical differences in terms of mortality in the ICU ([table 4](#)).

Among secondary infections, only fungal co-infections were significantly associated with death. In addition to the survival curves showing mortality to be significantly higher for CAPA patients ([figure 2](#)), invasive aspergillosis was associated with death in the univariate analysis ([table 4](#)), regardless of the case definition used: proven/probable/possible CAPA ($p<0.0001$), proven/probable CAPA ($p<0.0001$), possible CAPA ($p=0.01$), and proven/putative IPA ($p=0.011$). The detection of *Aspergillus* in respiratory samples by culture or PCR was also associated with death ($p=0.005$ and $p=0.05$, respectively, data not shown), regardless of the aspergillosis status. The introduction of anti-*Aspergillus* triazole (voriconazole and/or isavuconazole) did not modify mortality ([figure 3](#), $p=0.86$), nor did other antifungal drugs increase survival.

Aside from invasive *Aspergillus* infections, among the other infections, only candidemia was associated with mortality ($p=0.017$, [table 4](#)). There was no significance for bacterial VAP, nor HSV1 or CMV infections. We then performed a multivariate analysis of factors associated with death, which identified three significant factors: age ≥ 62 (HR 1.83 [95% CI 1.35-2.48]), solid organ transplantation (HR 2.33 [1.43-3.79], and proven/probable CAPA (HR 1.77 [1.25-2.48], [figure 4](#)). Of note, possible CAPA and candidemia, although not significantly associated with death, showed, however, a trend toward higher mortality (HR 1.37 [0.74-2.55] and 1.19 [0.71-2.01], respectively).

364 **Table 4. Baseline characteristics, host factors, treatments, and secondary infections**
 365 **associated with death in the intensive care unit (ICU) of 509 mechanically ventilated**
 366 **COVID-19 patients.**
 367

	Death in the ICU (n=186)	Survival (n=323)	
Factors (n, %)	n, %, (95% CI)	n, %, (95% CI)	p
Sex at birth			0.19
Female (109, 21%)	34, 18.3% (13.0-24.6)	75, 23.2% (18.7-28.2)	
Male (400, 79%)	152, 81.7% (75.4-87.0)	248, 76.8% (71.8-81.3)	
Age, years	62.3 ± 10.9	57.6 ± 13.1	0.0001
Mean ± SD, (95% CI)	(60.7-63.9)	(56.2-59.1)	
Weight, kg	86.8 ± 17.8	86.8 ± 17.5	0.93
Mean ± SD, (95% CI)	(84.2-89.5)	(85.0-88.9)	
BMI, kg/m ²	29.2 ± 5.6	29.3 ± 5.7	0.77
Mean ± SD, (95% CI)	(28.3-30.0)	(28.7-30.0)	
Baseline characteristics			
	n (%), [95% CI]		
Obesity (62, 12.2%)	17 9.1% (5.4-14.2)	45 13.9% (10.3-18.2)	0.11
Dyslipidemia (21, 4.1%)	8 4.3% (1.9-8.3)	13 4.0% (2.2-6.8)	0.88
Diabetes mellitus (167, 32.9%)	61 33.0% (26.3-40.3)	106 32.8% (27.7-38.2)	1.0
High blood pressure (254, 50.1%)	101 54.6% (47.1-61.9)	153 47.5% (42.0-53.1)	0.12
COPD (34, 6.7%)	17 9.1% (5.4-14.2)	17 5.3% (3.1-8.3)	0.09
Asthma (14, 2.8%)	8 4.3% (1.9-8.3)	6 1.9% (0.7-4.0)	0.10
Initial lymphopenia (323, 64.2%)	127 68.6% (61.4-75.3)	196 61.6% (56.0-67.0)	0.11
Transplantation (35, 6.9%)	22 11.8% (7.6-17.4)	13 4.0% (2.2-6.8)	0.0008
Hematological malignancy (6, 1.2%)	3 1.6% (0.3-4.7)	3 0.9% (0.2-2.7)	0.67
All immunosuppression (55, 10.8%)	28 15.1% (10.2-21.0)	27 8.4% (5.6-11.9)	0.019
Lopinavir+Ritonavir (Kaletra) (111, 21.8%)	50 26.9% (20.7-33.9)	61 18.9% (14.8-23.6)	0.035
Remdisivir (20, 3.9%)	7 3.8% (1.5-7.6)	13 4.0% (2.2-6.8)	0.88
Oseltamivir (40, 7.9%)	20 10.8% (6.7-16.1)	20 6.2% (3.8-9.4)	0.09
Cefotaxime (25, 4.9%)	1 0.5% (0.0-3.0)	24 7.4% (4.8-10.9)	0.0005
Rovamycin (15, 2.9%)	5 2.7% (0.9-6.2)	10 3.1% (1.5-5.6)	0.79
Azithromycin (10, 2.0%)	3 1.6% (0.3-4.6)	7 2.2% (0.9-4.4)	0.75
Hydroxychloroquine (167, 32.9%)	51 27.4% (21.1-34.4)	116 36.0% (30.8-41.5)	0.0502
Dexamethasone (202, 40.1%)	84 45.7% (38.3-53.1)	118 36.9% (31.6-42.4)	0.052
Anti-IL6 (38, 7.5%)	17 9.2% (5.4-14.3)	21 6.5% (4.1-9.8)	0.28
Anti-IL1	10	6	0.036

(16, 3.1%)	5.4% (2.6-9.7)	1.9% (0.7-4.0)	
Time in the ICU before mechanical ventilation (508)	186 0.1 ± 2.3 (-0.2-0.5)	322 -0.6 ± 5.6 (-1.2-0.00)	0.11
Duration of mechanical ventilation (508)	186 24.1 ± 16.6 (21.7-26.5)	322 28.9 ± 21.2 (26.5-31.2)	0.01
Prone position (394, 77.6%)	147 79.0% (72.5-84.6)	247 76.7% (71.7-81.2)	0.58

Clinical course data

Mean ± SD, median, and (95% CI)

SAPS II – admission (485, 44.1 ± 16.2)	180 46.8 ± 16.1 (44.4-49.2)	305 42.5 ± 16.1 (40.6-44.3)	0.004
SOFA – admission (398, 7.4 ± 3.9)	142 7.9 ± 3.9 (7.2-8.5)	256 7.2 ± 3.9 (6.7-7.6)	0.08
SOFA – day 7 (366 8.7 ± 4.2)	128 10.2 ± 4.1 (9.4-10.9)	239 7.9 ± 4.1 (7.4-8.4)	0.0001
SOFA – day 15 (261, 8.5 ± 4.6)	96 10.7 ± 4.1 (9.9-11.6)	165 7.1 ± 4.4 (6.5-7.8)	0.0001
SOFA - discharge (285, 6.1 ± 6.0)	109 12.6 ± 4.5 (11.7-13.4)	176 2.1 ± 2.1 (1.8-2.4)	0.0001
CAPA pr/pb/pos* (111, 21.8%)	63 33.9% (24.6-45.3)	48 14.8% (9.9-21.5)	<0.0001
CAPA pr/pb* (87, 17.1%)	52 28.0% (21.6-35.0)	35 10.8% (7.7-14.7)	<0.0001
CAPA pos* (24, 4.7%)	11 5.9% (3.0-10.3)	13 4.0% (2.2-6.8)	0.33
AI AspICU pr/pu# (57, 11.2%)	31 16.7% (11.6-22.8)	26 8.0% (5.3-11.6)	0.003
Other IFI (38, 7.5%)	21 11.3% (7.1-16.7)	17 5.3% (3.1-8.3)	0.013
Candidemia (32, 6.3%)	18 9.7% (5.8-14.9)	14 4.3% (2.4-7.2)	0.017
Bacterial VAP (374, 73.5%)	137 73.7% (66.7-79.8)	237 73.4% (68.2-78.1)	0.94
CMV infection (49, 10.0%)	22 12.2% (7.8-17.8)	27 8.7% (5.8-12.4)	0.22
HSV1 infection (76, 15.5%)	30 16.6% (11.5-22.8)	46 14.8% (11.1-19.3)	0.61

368
369
370

371 *Anti-IL6 treatment*

372 Among the 38 patients who received anti-IL6 for COVID-19, 15.3% were in the
 373 proven/probable/possible CAPA group versus 5.3% in the non-CAPA group ($p=0.0016$, **table**
 374 **3**). Comparison between only the proven/probable CAPA patients and the others showed a
 375 similar statistically significant difference ($p=0.006$). Although there was no significant link
 376 between anti-IL6 treatment and overall mortality (**table 4**), we investigated whether anti-IL6
 377 could be a significant onset factor for CAPA. The significant factors associated with anti-IL-6
 378 treatment by univariate analysis are summarized in **table 5**. Among them, four factors were
 379 identified by multivariate analysis. Dexamethasone treatment (6.64 [95% CI 2.89-15.23]),
 380 positive galactomannan antigenemia (5.01 [1.47-17.09]), and proven/probable/possible
 381 CAPA (2.60 [1.11-6.06]) were highly significantly associated with anti-IL6 treatment and an
 382 age ≥ 62 was significantly associated with the absence of anti-IL6 treatment (0.25 [0.11-
 383 0.58]).

384
385

386 **Table 5. Uni- and multivariate analysis of factors associated with anti-IL6 treatment in**
 387 **509 intubated and mechanically ventilated COVID-19 patients.**
 388

Factors	Anti-IL6 treatment	No anti-IL6	Univariate	Multivariate
	n (% [95% CI])	n (% [95% CI])	P	OR (95% CL)
Age, years	38	468	0.001	0.25
Mean \pm SD (95% CI)	53.1 \pm 12.8 (48.9 - 57.3)	59.9 \pm 12.3 (58.8 - 61.0)		(0.11-0.58) for age \geq 62
Solid organ transplantation	38	468	0.0383	-
Yes	6 (15.8% [6.0 - 31.3])	29 (6.2 [4.2% - 8.8])		
No	32 (84.2% [68.7 - 94.0])	439 (93.8% [91.2 - 95.8])		
Total immunodepression	38	468	0.0145	-
Yes	29 (76.3% [59.8 - 88.6])	46 (9.8% [7.3 - 12.9])		
No	9 (23.7% [11.4 - 40.2])	422 (90.2% [87.1 - 92.7])		
Dexamethasone	38	464	< 0.0001	6.64 (2.89-15.23)
Yes	29 (76.3% [59.8 - 88.6])	173 (37.3% [32.9 - 41.9])		
No	9 (23.7% [11.4 - 40.2])	291 (62.7% [58.1 - 67.1])		
<i>Aspergillus</i> culture in respiratory samples	38	468	0.040	-
Negative	29 (76.3% [59.8 - 88.6])	414 (88.5% [85.2 - 91.2])		
Positive	9 (23.7% [11.4 - 40.2])	54 (11.5% [8.8 - 14.8])		
Galactomannan antigenemia	38 (0)	468 (0)	0.002	5.01 (1.47-17.09)
Negative	31 (81.6% [65.7 - 92.3])	448 (95.7% [93.5 - 97.4])		
Positive	7 (18.4% [7.7 - 34.3])	20 (4.3% [2.6 - 6.5])		

Proven/Probable CAPA	38 (0)	468 (0)	0.004	-
No	25 (65.8% [48.6 - 80.4])	394 (84.2% [80.6 - 87.4])		
Yes	13 (34.2% [19.6 - 51.4])	74 (15.8% [12.6 - 19.4])		
Proven/probable/possible			0.002	2.60
CAPA	38 (0)	468 (0)		(1.11-6.06)
No	21 (55.3% [38.3 - 71.4])	374 (79.9% [76.0 - 83.5])		
Yes	13 (34.2% [19.6 - 51.4])	74 (15.8% [12.6 - 19.4])		
Among yes, possible	4 (10.5% [2.9 - 24.8])	20 (4.3 [2.6 - 6.5])		

389

390

391

392

393
394

DISCUSSION

395 To our knowledge, this is the largest cohort study to date to investigate the prevalence of IFI
396 among mechanically ventilated ICU patients infected with SARS-CoV-2, along with the
397 associated mortality and the risk factors for such secondary infections. Among this
398 homogeneous population, we were surprised to record 106/509 (20.8%) patients (representing
399 150 episodes) with proven or probable IFI, which increased to 130/509 (25.5%) when
400 including possible IFI. The high prevalence observed in the MYCOVID study may be related
401 to several factors, such as the homogeneous severe COVID-19 population with ARDS under
402 study, the rigorous monitoring dedicated to fungal diagnosis, the role of previous
403 comorbidities, and the role of the treatment received. Covid-19 associated aspergillosis are the
404 most prevalent fungal infections in this cohort. The vast majority of the already published data
405 included heterogeneous COVID-19 populations and mainly used the AspICU case definitions.
406 By contrast, we also used the recent CAPA definitions and included only the most severe
407 mechanically ventilated patients, which represents a higher-risk subgroup of patients than all
408 those infected with SARS-CoV-2. Using the most recent and consensual definitions in the
409 literature,⁸ we identified a high prevalence of CAPA. Indeed, we observed 17.1%
410 proven/probable CAPA and 4.7% possible CAPA cases, allowing us to refine the prevalence
411 of CAPA among mechanically ventilated COVID-19 patients. Highly variable IPA prevalence
412 estimates, ranging from 2% to 27.7%, have been reported in 10 studies that included more
413 than 80 patients.¹³⁻²² Such varying prevalence may be related to variable definitions of IPA,
414 the monocentric nature of most of the studies, and the relatively low number (<150) of
415 patients included in 8 of the 10 studies. Furthermore, the higher prevalence of IPA observed in
416 the MYCOVID study may be the result of under-diagnosis in previous studies, as several
417 authors did not provide their diagnostic criteria or rhythm of monitoring and used the AspICU
418 case definition.

419 We identified several factors associated with CAPA. Patients with CAPA were significantly
420 older, their disease was more severe based on the SOFA score on day 7, and they were more
421 frequently under immunosuppressive therapy, particularly for organ transplantation. They also
422 more frequently received anti-IL6 treatment, which was, furthermore, independently
423 associated with CAPA by multivariate analysis. The benefit/risk ratio of anti-IL6 treatment
424 needs to be carefully evaluated due to the conflicting results concerning its use and clinical
425 interest for COVID-19 patients.^{23, 24} Other risk factors, not investigated in this study, could be

426 linked to environmental exposure. Indeed, several teams have modified their existing air
427 treatment to protect healthcare workers from aerosolization by creating negative pressure
428 zones, which could potentially increase the risk of *Aspergillus* exposure.

429 Certain other respiratory viruses, such as influenza, also predispose patients to IPA.¹ In such
430 patients, infection by respiratory viruses results in epithelial damage and disruption of normal
431 ciliary clearance, aiding the invasion of pulmonary tissues by conidia. The prevalence of IPA
432 in patients infected with SARS-CoV-2 appears to be similar than the known prevalence
433 during severe seasonal influenza,¹ despite the accumulation of numerous facilitating factors,
434 including leucopenia/lymphopenia, T-cell perturbations, and treatment with corticosteroids,
435 anti-IL1, and anti-IL6.

436 One main result of this study is the significantly higher mortality of CAPA patients, both by
437 uni- and multivariate analysis, reaching 59·8% for proven/probable and 45·8% for possible
438 CAPA versus 30·9 in the absence of CAPA. One limit to this work is that it was not designed
439 to evaluate the efficacy of antifungal treatment. Such elevated mortality warrants
440 consideration of early antifungal strategies, such as antifungal prophylaxis for high-risk
441 patients, as well as the implementation of air-treatment measures. Of note, we observed a
442 pejorative outcome using the AspICU classification for proven/putative AI (31/57, 54·4%)
443 similar to that for proven/probable CAPA (52/87, 59·8%), even for patients categorized as
444 colonized (18/50, 36%), compared to non-CAPA patients. A search for discrepancies in the
445 classification between CAPA and AspICU case definitions showed that 36 patients classified
446 as CAPA were classified as “only” colonized using the AspICU case definition. Mortality
447 was, however, as high as 61·1% (22/36). Although many authors have suggested that the
448 presence of *Aspergillus* in respiratory specimens from COVID-19-infected patients is a
449 manifestation of colonization, we advocate using the more robust CAPA definitions and
450 considering any marker indicating the presence of *Aspergillus* as an indication to perform a
451 BAL, as also suggested by van Grootveld.²⁵ In the MYCOVID study, all positive diagnostic
452 procedures on respiratory and/or blood samples were statistically linked to increased mortality
453 and should be considered.

454 Aside from aspergillosis, the MYCOVID study highlights the occurrence of other fungal
455 infections, with a high prevalence of 7·5%, of which the most frequent was candidemia in
456 6·3% of patients. Several authors have noted a global increase in the incidence of candidemia
457 in COVID-19 patients, even candidemia due to *Candida auris*.^{26, 27} Among them, a recent

458 review reported an overall incidence varying from 0·7% to 23·5%, of which most occurred in
459 the ICU.²⁶ The reasons for such an increased incidence in this specific population is as yet
460 unknown. COVID-19 patients are exposed to multiple risk factors for candidemia, such as
461 antibiotic therapy, corticosteroids, immunosuppressive therapy, and long ICU stays. Several
462 studies have suggested that direct disruption of the intestinal barrier caused by COVID-19
463 may be an additional risk factor for candidemia.^{21, 28} Indeed, it is known that enterocytes are
464 infected by SARS-CoV-2, suggesting a possible link with *Candida* gut translocation.²⁹
465 Recently, a pilot study found enrichment of the fecal mycobiome with *Candida* and
466 *Aspergillus* during the hospitalization of 30 patients with COVID-19 relative to controls.³⁰
467 However, more studies are needed to determine whether such alterations can explain the
468 observed increased incidence of candidemia. The high mortality of patients with candidemia
469 in the MYCOVID study (56·3%) warrants the analysis of risk factors and the establishment of
470 optimal management and prevention of candidemia in this context.

471 This study highlights the high prevalence and mortality of invasive aspergillosis and
472 candidiasis in ARDS-associated COVID-19 patients relative to that due to bacterial and viral
473 secondary infections.

474 Antifungal drugs with high efficacy and low toxicity are available, along with non-invasive
475 diagnostic tools, to allow the efficient management of IFI. The high mortality currently
476 associated with CAPA demonstrates the importance of improving the management of this
477 infectious complication. Overall, these findings highlight the need for a high index of
478 suspicion and the implementation of active surveillance.

479 Further studies should determine if an early antifungal treatment or prophylaxis is needed if
480 risk factors, such as those determined in this study, are present.

481

482

483 **Contributors**

484 JPG, ED, JRZ, and MEB conceived and designed the trial and wrote the manuscript. BL and
485 JM contributed to the protocol and design of the study. All other authors contributed to the
486 implementation of the study, inclusion of patients, and data collection. All authors critically
487 reviewed and approved the final version.

488

489 **Declaration of interests**

490

491 **Acknowledgments**

492 We thank

493 Relecture, stats, We also thank the volunteers who participated in this study.

494

495 **Figure legends**

496 **Figure 1.** Study design (A) and study flowchart (B)

497 **Figure 2.** Survival probability according to CAPA status

498 **Figure 3.** Probability of survival of proven/probable/possible CAPA patients receiving, or
499 not, anti-*Aspergillus* treatment with voriconazole and/or isavuconazole

500 **Figure 4.** Multivariate analysis of factors associated with death

501

502

503

504

505

506

507 **References**

- 508 1 Schauwvlieghe A, Rijnders BJA, Philips N, et al. Invasive aspergillosis in patients
509 admitted to the intensive care unit with severe influenza: a retrospective cohort study.
510 *Lancet Respir Med* 2018; **6**: 782-92.
- 511 2 Verweij PE, Rijnders BJA, Bruggemann RJM, et al. Review of influenza-associated
512 pulmonary aspergillosis in ICU patients and proposal for a case definition: an expert
513 opinion. *Intensive Care Med* 2020; **46**: 1524-35.
- 514 3 Bassetti M, Kollef MH, Timsit JF. Bacterial and fungal superinfections in critically ill
515 patients with COVID-19. *Intensive Care Med* 2020; **46**: 2071-4.
- 516 4 Lai CC, Yu WL. COVID-19 associated with pulmonary aspergillosis: a literature
517 review. *J Microbiol Immunol Infect* 2021; **54**: 46-53.
- 518 5 Apostolopoulou A, Esquer Garrigos Z, Vijayvargiya P, Lerner AH, Farmakiotis D.
519 Invasive pulmonary aspergillosis in patients with SARS-CoV-2 infection: a systematic
520 review of the literature. *Diagnostics (Basel)* 2020; **10**: 807.
- 521 6 Arastehfar A, Carvalho A, van de Veerdonk FL, et al. COVID-19 associated pulmonary
522 aspergillosis (CAPA)-from immunology to treatment. *J Fungi (Basel)* 2020; **6**: 91.
- 523 7 Marr KA, Platt A, Tornheim JA, et al. Aspergillosis complicating severe coronavirus
524 disease. *Emerg Infect Dis* 2021; **27**: 18-25.
- 525 8 Koehler P, Bassetti M, Chakrabarti A, et al. Defining and managing COVID-19-
526 associated pulmonary aspergillosis: the 2020 ECMM/ISHAM consensus criteria for
527 research and clinical guidance. *Lancet Infect Dis* 2020; published online Dec 14.
528 [https://doi.org/10.1016/s1473-3099\(20\)30847-1](https://doi.org/10.1016/s1473-3099(20)30847-1).
- 529 9 Donnelly JP, Chen SC, Kauffman CA, et al. Revision and update of the consensus
530 definitions of invasive fungal disease from the European Organization for Research and
531 Treatment of Cancer and the Mycoses Study Group Education and Research
532 Consortium. *Clin Infect Dis* 2020; **71**: 1367-76.
- 533 10 Bassetti M, Giacobbe DR, Grecchi C, et al. Performance of existing definitions and tests
534 for the diagnosis of invasive aspergillosis in critically ill, adult patients: a systematic
535 review with qualitative evidence synthesis. *J Infect* 2020; **81**: 131-46.
- 536 11 Blot SI, Taccone FS, Van den Abeele AM, et al. A clinical algorithm to diagnose
537 invasive pulmonary aspergillosis in critically ill patients. *Am J Respir Crit Care Med*
538 2012; **186**: 56-64.
- 539 12 Machado M, Valerio M, Alvarez-Uria A, et al. Invasive pulmonary aspergillosis in the
540 COVID-19 era: an expected new entity. *Mycoses* 2021; **64**: 132-43.
- 541 13 Bartoletti M, Pascale R, Cricca M, et al. Epidemiology of invasive pulmonary
542 aspergillosis among COVID-19 intubated patients: a prospective study. *Clin Infect Dis*
543 2020; published online Jul 28. <https://doi.org/10.1093/cid/ciaa1065>.
- 544 14 Dellière S, Dudoignon E, Fodil S, et al. Risk factors associated with COVID-19-
545 associated pulmonary aspergillosis in ICU patients: a French multicentric retrospective
546 cohort. *Clin Microbiol Infect* 2020; published online Dec 13.
547 <https://doi.org/10.1016/j.cmi.2020.12.005>.
- 548 15 Dupont D, Menotti J, Turc J, et al. Pulmonary aspergillosis in critically ill patients with
549 Coronavirus Disease 2019 (COVID-19). *Med Mycol* 2021; **59**: 110-4.
- 550 16 Fekkar A, Lampros A, Mayaux J, et al. Occurrence of invasive pulmonary fungal
551 infections in patients with severe COVID-19 admitted to the ICU. *Am J Respir Crit*
552 *Care Med* 2021; **203**: 307-17.

- 553 17 Lamoth F, Glampedakis E, Boillat-Blanco N, Oddo M, Pagani JL. Incidence of invasive
554 pulmonary aspergillosis among critically ill COVID-19 patients. *Clin Microbiol Infect*
555 2020; **26**: 1706-8.
- 556 18 Maes M, Higginson E, Pereira-Dias J, et al. Ventilator-associated pneumonia in
557 critically ill patients with COVID-19. *Crit Care* 2021; **25**: 25.
- 558 19 Razazi K, Arrestier R, Haudebourg AF, et al. Risks of ventilator-associated pneumonia
559 and invasive pulmonary aspergillosis in patients with viral acute respiratory distress
560 syndrome related or not to Coronavirus 19 disease. *Crit Care* 2020; **24**: 699.
- 561 20 Ripa M, Galli L, Poli A, et al. Secondary infections in patients hospitalized with
562 COVID-19: incidence and predictive factors. *Clin Microbiol Infect* 2021; **27**: 451-7.
- 563 21 White PL, Dhillon R, Cordey A, et al. A national strategy to diagnose COVID-19
564 associated invasive fungal disease in the ICU. *Clin Infect Dis* 2020; published online
565 Aug 29. <https://doi.org/10.1093/cid/ciaa1298>.
- 566 22 Permpalung N, Chiang TP, Massie AB, et al. COVID-19 associated pulmonary
567 aspergillosis in mechanically ventilated patients. *Clin Infect Dis* 2021; published online
568 Mar 9. <https://doi.org/10.1093/cid/ciab223>.
- 569 23 Stone JH, Frigault MJ, Serling-Boyd NJ, et al. Efficacy of tocilizumab in patients
570 hospitalized with Covid-19. *N Engl J Med* 2020; **383**: 2333-44.
- 571 24 Horby PW, Pessoa-Amorim G, Peto L, et al. Tocilizumab in patients admitted to
572 hospital with COVID-19 (RECOVERY): preliminary results of a randomised,
573 controlled, open-label, platform trial. *medRxiv* 2021: 2021.02.11.21249258.
- 574 25 van Grootveld R, van Paassen J, de Boer MGJ, et al. Systematic screening for COVID-
575 19 associated invasive aspergillosis in ICU patients by culture and PCR on tracheal
576 aspirate. *Mycoses* 2021; published online Feb 19. <https://doi.org/10.1111/myc.13259>.
- 577 26 Nucci M, Barreiros G, Guimarães LF, Deriquehem VAS, Castiñeiras AC, Nouér SA.
578 Increased incidence of candidemia in a tertiary care hospital with the COVID-19
579 pandemic. *Mycoses* 2021; **64**: 152-6.
- 580 27 Prestel C, Anderson E, Forsberg K, et al. *Candida auris* outbreak in a COVID-19
581 specialty care unit - Florida, July-August 2020. *MMWR Morb Mortal Wkly Rep* 2021;
582 **70**: 56-7.
- 583 28 Mastrangelo A, Germinario BN, Ferrante M, et al. Candidemia in COVID-19 patients:
584 incidence and characteristics in a prospective cohort compared to historical non-
585 COVID-19 controls. *Clin Infect Dis* 2020; published online Oct 30.
586 <https://doi.org/10.1093/cid/ciaa1594>.
- 587 29 Xiao F, Tang M, Zheng X, Liu Y, Li X, Shan H. Evidence for gastrointestinal infection
588 of SARS-CoV-2. *Gastroenterology* 2020; **158**: 1831-3 e3.
- 589 30 Zuo T, Zhan H, Zhang F, et al. Alterations in fecal fungal microbiome of patients with
590 COVID-19 during time of hospitalization until discharge. *Gastroenterology* 2020; **159**:
591 1302-10.e5.

592
593

594
595
596
597
598
599

600 Koehler Philip

601 MARR Kierien, University of Seattle

602 Benoit Misset

603 Frédéric Lamothe
604 Stijn Blot, University of Gant
605 Vanderdonk
606 D Denning, University of Manchester
607 TORRES Antonio, University of Barcelona
608 Rodriguez-Bano Jesus, University of Sevilla
609 MUNOZ P, University of Madrid
610 WELTE Tobias, University School of Hanver
611 SHORR Andrew, Washington Dc,
612 KANJ Souha, American University of Beirut
613
614