Invasive pulmonary aspergillosis among intubated patients with SARS-CoV-2 or influenza pneumonia: a European multicenter comparative cohort study

Anahita Rouzé1,2, Elise Lemaître1, Ignacio Martin-Loeches3,4,5, Pedro Povoa6,7,8, Emili Diaz9, Rémy Nyga10, Antoni Torres11, Matthieu Metzelard10, Damien Du Cheyron12, Fabien Lambiotte13, Fabienne Tamion14, Marie Labrure15, Claire Boulle Geronimi16, Charles-Edouard Luyt17, Martine Nyunga18, Olivier Pouly19, Arnaud W. Thille20, Bruno Megarbane21, Anastasia Saade22, Eleni Magira23, Jean-François Llitjos24, Iliana Ioannidou25, Alexandre Pierre26, Jean Reignier27, Denis Garoë28, Louis Kreitmann29, Jean-Luc Baudel30, Guillaume Voiriot31, Gaëtan Plantefeve32, Elise Morawiec33,34, Pierre Asfar35, Alexandre Boyer36, Armand Mekontso-Dessap37, Demosthenes Makris38, Christophe Vinsonneau39, Pierre-Edouard Floch40, Clémence Marois41,42, Adrian Ceccato43, Antonio Artigas44, Alexandre Gaudet1,45, David Nora6, Marjorie Cornu2,46, Alain Duhamel47,48, Julien Labreuche47,48, Saad Nseir1,2* and the coVAPid study group

Abstract

Background: Recent multicenter studies identified COVID-19 as a risk factor for invasive pulmonary aspergillosis (IPA). However, no large multicenter study has compared the incidence of IPA between COVID-19 and influenza patients.

Objectives: To determine the incidence of putative IPA in critically ill SARS-CoV-2 patients, compared with influenza patients.

Methods: This study was a planned ancillary analysis of the coVAPid multicenter retrospective European cohort. Consecutive adult patients requiring invasive mechanical ventilation for > 48 h for SARS-CoV-2 pneumonia or influenza pneumonia were included. The 28-day cumulative incidence of putative IPA, based on Blot definition, was the primary outcome. IPA incidence was estimated using the Kalbfleisch and Prentice method, considering extubation (dead or alive) within 28 days as competing event.

Results: A total of 1047 patients were included (566 in the SARS-CoV-2 group and 481 in the influenza group). The incidence of putative IPA was lower in SARS-CoV-2 pneumonia group (14, 2.5%) than in influenza pneumonia group (29, 6%), adjusted cause-specific hazard ratio (cHR) 3.29 (95% CI 1.53–7.02, p = 0.0006). When putative IPA and Aspergillus respiratory tract colonization were combined, the incidence was also significantly lower in the SARS-CoV-2 group, as compared to influenza group (4.1% vs. 10.2%), adjusted cHR 3.21 (95% CI 1.88–5.46, p < 0.0001). In the whole patient group, the incidence was significantly lower in SARS-CoV-2 group (1.4% vs. 4.7%, adjusted cHR 3.12 (95% CI 1.76–5.55, p < 0.0001).

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Background
Invasive pulmonary aspergillosis (IPA) was reported to be common in critically ill patients with chronic obstructive pulmonary disease (COPD) [1], acute respiratory distress syndrome (ARDS) [2], cirrhosis [3], acute hepatitis [4], or immunosuppression [5]. Previous studies also highlighted a relationship between IPA and outcomes, including mortality, duration of mechanical ventilation, and ICU length of stay [6]. Recently, critically ill patients receiving invasive mechanical ventilation for severe influenza were identified as a high-risk population for IPA [7]. Influenza-associated IPA (IAPA) was also reported to be associated with increased risk for mortality in this population.

Case series, rapidly followed by single-center and large multicenter studies, highlighted a link between COVID-19 pneumonia and IPA. The incidence of IPA ranges from 4.8 to 23% of patients with SARS-CoV-2 pneumonia receiving invasive mechanical ventilation [8–17]. Some of these studies also showed that COVID-19-associated IPA (CAPA) was associated with increased mortality and longer duration of mechanical ventilation, and ICU stay [16]. To the best of our knowledge, only one retrospective study compared the incidence of IPA between COVID-19 ARDS patients and other-viruses-related ARDS [18]. This study suggested that COVID-19 was associated with reduced incidence of IPA as compared to other ARDS patients. However, the number of included patients was limited (n = 172) and the study was performed in a single center.

Therefore, we conducted this planned ancillary study of the coVAPid European multicenter cohort to determine the incidence of putative IPA in SARS-CoV-2 pneumonia, compared to influenza pneumonia, in intubated critically ill patients. Secondary objectives were to determine the impact of putative IPA on morbidity and mortality, and the incidence of probable IPA, based on Verweij definition [19].

Methods

Study design and population
This study was a planned ancillary analysis of the coVAPid multicenter retrospective observational cohort, conducted in 36 ICUs in Europe. The methods used in the coVAPid study are described elsewhere [20]. Briefly, consecutive adult patients with SARS-CoV-2 pneumonia, influenza pneumonia, or no viral infection at ICU admission, who required invasive mechanical ventilation for more than 48 h, were included. Only patients with SARS-CoV-2 pneumonia, or influenza pneumonia, were eligible for the current ancillary study. Patients with missing data regarding the primary outcome were excluded from the current analysis.

The Ethics Committee and Institutional Review Board of the Lille University Hospital approved the study protocol (Comité de Protection des Personnes Ouest VI; approved by April 14, 2020; registration number RIPH:20.04.09.60039) as minimal-risk research using data collected for routine clinical practice and waived the requirement for informed consent. Patients (or their proxies) received written information about the study and could refuse to participate. The study was registered at ClinicalTrials.gov, number NCT04359693.

Definitions
Blot criteria were used for IPA diagnosis, as primary outcome [21]. When at least one criterion necessary for the diagnosis of putative IPA according to Blot definition was not met, the case was classified as Aspergillus colonization. Verweij criteria were used for probable IPA diagnosis, as a secondary outcome (Additional file 1: Table E1) [19]. Suspected IPA refers to clinical suspicion associated with any positive serum or respiratory sample for Aspergillus.

Outcomes
The primary outcome of our study was the incidence of putative IPA, according to Blot definition. The secondary outcomes included the incidence of probable IPA, according to Verweij definition; and outcomes of putative IPA, including mechanical ventilation duration, ICU length of stay, and 28-day mortality.

Statistical analysis
Quantitative variables were expressed as median (interquartile range) and categorical variables were expressed as numbers (percentage). Patient characteristics at ICU admission and during ICU stay were described, in each
group, according to aspergillosis status (none, Aspergil-
lus colonization, and putative IPA), without formal sta-
tistical comparisons. The 28-day cumulative incidence of
putative or probable IPA, or combination of colonization
and putative IPA were estimated using Kalbfleisch and
Prentice method, considering extubation (dead or alive)
within 28 days as competing event. For the incidence of
putative IPA according to Blot definition, occurrence
of Aspergillus colonization was treated as a competing
event, in addition to extubation [22].

Regarding the causal relationship of interest, we
assessed the association of study groups with IPA
(according to both definitions, as well as combining
together colonization and putative IPA) using cause-
specific Cox’s proportional hazard models, with sand-
wich covariance estimation to account for center
clustering effect. We considered previously cited compet-
ing events, before and after adjustment for pre-specified
confounders (simplified acute physiology score (SAPS) II,
COPD, immunosuppression, recent antibiotic treatment
before ICU admission, ARDS on admission, corticos-
teroid treatment during ICU stay) [23]. Cause-specific
hazard ratios (cHR) and their 95% confidence intervals
(CIs) associated with SARS-CoV-2 pneumonia, against
influenza pneumonia, were derived from Cox’s models as
effect sizes.

We assessed the association of putative IPA with
patient’s outcomes censored at day 28 (overall survival,
mechanical ventilation duration, length of ICU stay)
using a Cox’s regression model (with sandwich covari-
cestimation to account for center clustering effect)
performed on the whole study population, combining
the two groups), with cause-specific hazard for mecha-
nical ventilation duration (considering extubation alive as
event of interest and death under mechanical ventilation
as competing event), and for length of ICU stay (con-
sidering ICU discharge alive as event of interest, and
death during ICU as competing event), including study
group, IPA, and interaction between IPA status and study
group. IPA was treated as a time-dependent covariate, as

![Flowchart](image-url)

Fig. 1 Flowchart. Suspected IPA refers to clinical suspicion associated with any positive serum or respiratory sample for Aspergillus. Putative IPA and
Aspergillus colonization are defined according to Blot definition. IPA, invasive pulmonary aspergillosis
| Table 1 | Patient characteristics at ICU admission according to study group and aspergillosis status based on Blot definition |
|---------|---------------------------------------------------------------------------------------------------------------|
|         | **SARS-CoV-2 pneumonia**                                                                                      | **Influenza pneumonia**                                                                 |
|         | $n = 566$                                                                                                      | $n = 481$                                                                                   |
|         | **No putative IPA, or colonization** $(n = 543)$                                                                | **No putative IPA, or colonization** $(n = 432)$                                             |
|         | **Aspergillus colonization** $(n = 9)$                                                                          | **Aspergillus colonization** $(n = 20)$                                                     |
|         | **Putative IPA**                                                                                               | **Putative IPA**                                                                             |
| Age, years | 64 (55 to 71)                                                                                                  | 62 (53 to 71)                                                                               |
| Men | 387/543 (71.3)                                                                                                 | 271/432 (62.7)                                                                              |
| Body mass index, kg/m² | 28.7 (25.7 to 33.6)                                                                                           | 29.0 (25.7 to 30.4)                                                                         |
| Severity scores |                                                                                                                |                                                                                             |
| SAPS II | 41 (32 to 56)                                                                                                  | 50 (39 to 64)                                                                               |
| SOFA score | 6 (3 to 8)                                                                                                    | 8 (6 to 11)                                                                                |
| Comorbidities scores |                                                                                                                |                                                                                             |
| McCabe classification |                                                                                                                |                                                                                             |
| Non-fatal | 454/518 (87.6)                                                                                                 | 288/410 (70.2)                                                                              |
| Fatal < 5 years | 58/518 (11.2)                                                                                                 | 107/410 (26.1)                                                                             |
| Fatal < 1 year | 6/518 (1.2)                                                                                                   | 119/410 (29.7)                                                                             |
| Charlson Comorbidity Index |                                                                                                                |                                                                                             |
| Chronic diseases |                                                                                                                |                                                                                             |
| Diabetes mellitus | 159/540 (29.4)                                                                                                 | 94/425 (22.1)                                                                              |
| Chronic kidney disease | 29/535 (5.4)                                                                                                   | 1/20 (5.0)                                                                                 |
| Heart disease | 98/535 (18.3)                                                                                                   | 3/20 (15.0)                                                                                |
| Chronic heart failure | 19/534 (3.6)                                                                                                   | 119/426 (27.9)                                                                             |
| COPD | 35/536 (6.5)                                                                                                    | 7/20 (35.0)                                                                                |
| Chronic respiratory failure | 19/534 (3.6)                                                                                                   | 2/14 (14.3)                                                                                |
| Cirrhosis | 8/535 (1.5)                                                                                                     | 1/14 (7.1)                                                                                 |
| Hematological malignancy | 46/535 (8.6)                                                                                                   | 1/14 (7.1)                                                                                 |
| Solid cancer | 25/534 (4.7)                                                                                                   | 24/428 (5.6)                                                                               |
| Organ transplant | 5/534 (0.9)                                                                                                    | 7/248 (1.6)                                                                                |
| HIV | 3/534 (0.6)                                                                                                     | 5/428 (1.2)                                                                                |
| Active smoking | 29/536 (5.4)                                                                                                   | 44/428 (10.3)                                                                              |
| Alcohol abuse | 33/534 (6.2)                                                                                                   | 130/426 (30.5)                                                                             |
| Location before ICU admission |                                                                                                                |                                                                                             |
| Home | 264/543 (48.6)                                                                                                  | 251/431 (58.2)                                                                              |
| Hospital ward | 199/543 (36.6)                                                                                                 | 138/431 (32.0)                                                                              |
| Another ICU | 80/543 (14.7)                                                                                                   | 42/431 (9.7)                                                                               |
| Recent hospitalization (<3 months) | 39/541 (7.2)                                                                                                   | 61/429 (14.2)                                                                              |
| Recent antibiotics (<3 months) | 70/542 (12.9)                                                                                                  | 79/427 (18.5)                                                                              |
| Hospital to ICU admission, days | 1 (0 to 2)                                                                                                      | 251/431 (58.2)                                                                              |
| Hospital admission to intubation, days | 1 (0 to 3)                                                                                                     | 138/431 (32.0)                                                                              |
| Antibiotic treatment on ICU admission | 1 (0 to 2)                                                                                                      | 42/431 (9.7)                                                                               |
| Causes for ICU admission |                                                                                                                |                                                                                             |
| Shock | 99/534 (18.5)                                                                                                   | 369/421 (87.6)                                                                             |
| Acute respiratory failure | 500/542 (92.3)                                                                                                 | 12/14 (85.7)                                                                               |
3-levels categorical variable: no putative IPA or Aspergillus colonization, versus Aspergillus colonization, and putative IPA. This model accounted for exposure time of IPA, by comparing at each follow-up time event point, the current IPA status of patients who have the event to patients who are at risk (without the event of interest and without the competing event for mechanical ventilation duration and length of ICU stay). The associations were further adjusted for the same previously mentioned confounders [24].

Statistical testing was performed at the two-tailed α level of 0.05. Data were analyzed using the SAS software package, release 9.4 (SAS Institute, Cary, NC).

### Results

#### Patient characteristics at ICU admission

In total, 1047 patients were included (Fig. 1). Percentage of men, ARDS, and body mass index were higher in SARS-CoV-2 group than in influenza group. SAPS II, sequential organ failure assessment (SOFA) score, comorbidity scores, chronic diseases, rate of recent hospitalization, shock, cardiac arrest, neurological failure, or acute kidney injury were lower in SARS-CoV-2 pneumonia group, as compared to influenza pneumonia group (Table 1). The distribution of study patients in different centers is presented in Additional file 1: Table E3.

#### Patient characteristics during ICU stay

Percentage of prone positioning, as well as total duration of antimicrobial treatment were higher in SARS-CoV-2 pneumonia group than in influenza pneumonia group. Corticosteroid use, ECMO, and 28-day mortality rates were comparable in the two groups. The dose of corticosteroids was higher in SARS-CoV-2 pneumonia group, as compared to influenza group (Table 2).

#### Incidence of putative IPA according to Blot definition

Seventy-two patients, from 25 out of 36 participating centers, were suspected by clinicians as having IPA, including 23 in SARS-CoV-2 group, and 49 in influenza group. Of these 72 patients, 43 were classified as putative IPA, and 29 as Aspergillus colonization, according to Blot definition. No proven IPA was diagnosed in study patients.

The incidence of putative IPA was significantly lower in SARS-CoV-2 pneumonia group than in influenza pneumonia group (Fig. 2A, Table 3). This difference remained significant after adjustment for confounding factors. Similarly, when combining putative IPA and Aspergillus respiratory tract colonization, the incidence was still significantly lower in SARS-CoV-2 group than in influenza group (Fig. 3, Table 3). The classification of study patients, based on different definitions, is presented in Additional file 1: Table E2.

#### Incidence of probable IPA according to Verweij definition

Among the 72 patients suspected by physicians as having IPA, 58 patients were classified as probable IPA according to Verweij definition. The incidence of probable IPA was also significantly lower in SARS-CoV-2 group, as compared to influenza group (Fig. 2B, Table 3). This difference remained significant after adjustment for confounding factors at ICU admission.
Outcomes of putative IPA

In the whole study population, putative IPA was associated with significant increase in 28-day mortality rate, and length of ICU stay, compared with colonized patients, or those with no IPA or Aspergillus colonization. These results were not confirmed in the subgroups of patients with SARS-CoV-2 or influenza pneumonia. Only in influenza group, duration of mechanical ventilation, and ICU stay were significantly longer in patients with putative IPA, as compared with those with no putative IPA or Aspergillus colonization (Fig. 4).

Characteristics of patients with putative IPA

Median time from intubation to putative IPA diagnosis was longer in SARS-CoV-2 than in influenza group (11 vs. 6 days). Bronchoalveolar lavage was less frequently performed and antifungal treatment was less frequently prescribed in SARS-CoV-2 than in influenza group (Table 4).

Discussion

Overall, the incidence of putative IPA was low in patients with COVID-19 or influenza. Further, putative IPA incidence was significantly lower in SARS-CoV-2 pneumonia patients than in those with influenza pneumonia. Similar results were found regarding probable IPA, using Verweij definition. Putative IPA was associated with significantly higher 28-day mortality rate and length of ICU stay, compared with colonized patients, or those with no IPA or Aspergillus colonization. However, IPA was not significantly associated with increased duration of mechanical ventilation.

Incidence of invasive pulmonary aspergillosis

The incidence of IPA was low in our study, and some previous studies reported higher incidence of IAPA and CAPA [7, 12–14, 16, 17]. However, in most of these studies, screening for IPA was performed routinely. Further,
Fig. 2  Cumulative incidence of putative or probable invasive pulmonary aspergillosis according to Blot (A) and Verweij (B) definitions. Cumulative incidence was estimated using Kalbfleisch and Prentice method, considering extubation (alive or due to death) within 28 days as competing event. Time axis starts at the day of intubation. IPA, invasive pulmonary aspergillosis, MV, mechanical ventilation.
Table 3  Incidence of invasive pulmonary aspergillosis

|                          | SARS-CoV-2 pneumonia n = 566 | Influenza pneumonia n = 481 | Unadjusted cHR (95% CI) | Adjusted cHR* (95% CI) | p value* |
|--------------------------|------------------------------|-----------------------------|-------------------------|------------------------|----------|
| **Blot definition**      |                              |                             |                         |                        |          |
| Putative invasive pulmonary aspergillosis | 14/566 (2.5) | 29/481 (6.0) | 3.07 (1.52 to 6.19) | 3.29 (1.53 to 7.02) | 0.0006   |
| Putative invasive pulmonary aspergillosis or Aspergillus colonization | 23/566 (4.1) | 49/481 (10.2) | 3.17 (1.87 to 5.35) | 3.21 (1.88 to 5.46) | <0.0001  |
| **Verweij definition**   |                              |                             |                         |                        |          |
| Probable invasive pulmonary aspergillosis | 17/566 (3.0) | 41/481 (8.5) | 3.54 (1.86 to 6.73) | 3.78 (1.96 to 7.27) | <0.0001  |

Values are number of invasive pulmonary aspergillosis (28-day cumulative incidence expressed as %, considering extubation (dead or alive) as a competing event). cHR calculated using cause-specific Cox's proportional hazard model with sandwich covariance estimation to account for center clustering effect. *Adjusted for pre-specified confounders (simplified acute physiology score II, chronic obstructive pulmonary disease, immunosuppression, recent antibiotic treatment, acute respiratory distress syndrome, corticosteroid treatment), and calculated after handling missing values on covariates by multiple imputation. cHR, cause-specific hazard ratio; CI, confidence interval.

Fig. 3  Cumulative incidence of putative invasive pulmonary aspergillosis or Aspergillus colonization according to Blot definition. Cumulative incidence was estimated using Kalbfleisch and Prentice method, considering extubation (alive or due to death) within 28 days as competing event. Time axis starts at the day of intubation. IPA, invasive pulmonary aspergillosis, MV, mechanical ventilation.
patients with no routine screening were excluded. For example, in the recent multicenter Mycovid study [16], only patients with at least 3 screening samples performed within 2 weeks were analyzed, which resulted in overestimating the reported incidence of CAPA (15%). The population at risk are all patients receiving mechanical ventilation, and not only those receiving >2 weeks of invasive mechanical ventilation. Another potential explanation for the high incidence of IPA reported in these studies is the false positive results of galactomannan in some patients, which is supported by the absence of positive impact of antifungal treatment on mortality, and the fact that some patients with CAPA survived in spite of absence of any antifungal treatment [13]. On the other hand, other well-performed single and multicenter studies reported lower incidence of IPA in influenza and COVID-19 patients [9, 10, 18, 25], which is in line with our findings. Geographical distribution and different case definitions might explain the variation in IPA incidence.

Comparison of invasive pulmonary aspergillosis incidence between COVID-19 and influenza patients

Our results suggest that IPA incidence might be lower in COVID-19 patients, compared with influenza patients. Several explanations could be provided for this result. First, the percentage of patients with immunosuppression at ICU admission was lower in COVID-19 than in influenza patients (8.8% vs. 22%). However, adjustment was performed for immunosuppression, as well as for other potential confounders. Second, BAL was performed less frequently in COVID-19 than in influenza patients, which might have underestimated the incidence of IPA in the first group. This could be explained by the fear of SARS-CoV-2 aerosolization and transmission to health workers at the beginning of the pandemic. Other factors, such as most severe ARDS, and more common prone position use in COVID-19 than in influenza patients could also explain the lower rate of BAL in COVID-19 patients. Third, the mechanism of entry of SARS-CoV-2, and influenza into the lower respiratory tract, and the
### Table 4  Characteristics of patients with putative invasive pulmonary aspergillosis, according to Blot definition

|                                      | SARS-CoV-2 pneumonia | Influenza pneumonia |
|--------------------------------------|-----------------------|---------------------|
| **Time from hospital admission to IPA diagnosis** | 12 (7 to 14)          | 9 (6 to 11)         |
| **Time from ICU admission to IPA diagnosis** | 11 (5 to 13)          | 6 (2 to 10)         |
| **Time from intubation to IPA diagnosis** | 11 (4 to 12)          | 6 (2 to 10)         |
| **Clinical presentation at the time of IPA diagnosis** |                         |                     |
| Hemoptysis                           | 2/14 (14.3)           | 4/29 (13.8)         |
| Respiratory worsening                 | 14/14 (100.0)         | 24/29 (82.8)        |
| New or increased fever                | 12/14 (85.7)          | 15/29 (51.7)        |
| **Imaging at the time of IPA diagnosis** |                         |                     |
| Abnormal medical imaging (chest X-ray or CT scan) | 14/14 (100.0)         | 29/29 (100.0)       |
| **Predominant lesion on chest CT:**   |                       |                     |
| Dense, well-circumscribed lesion with or without a halo sign | 0/5 (0.0)             | 3/23 (13.0)         |
| Air-crescent sign                     | 0/5 (0.0)             | 0/23 (0.0)          |
| Cavity                               | 0/5 (0.0)             | 2/23 (8.7)          |
| Segmental or lobar consolidation     | 3/5 (60.0)            | 9/23 (39.1)         |
| Other                                | 2/5 (40.0)            | 9/23 (39.1)         |
| **Serum samples during ICU stay**    |                       |                     |
| Galactomannan index ≥ 0.5            | 6/12 (50.0)           | 20/26 (76.9)        |
| Galactomannan index at the time of IPA diagnosis | 0.2 (0.0 to 0.6)      | 0.2 (0.1 to 1.4)    |
| Highest Galactomannan index          | 0.2 (0.1 to 0.8)      | 0.5 (0.1 to 1.4)    |
| 1,3-β-D-glucan level at time of IPA diagnosis (pg/mL) | 63 (30 to 450)        | 111 (47 to 384)     |
| Highest level of 1,3-β-D-glucan (pg/mL) | 170 (39 to 760)       | 178 (56 to 501)     |
| **Respiratory samples leading to IPA diagnosis** |               |                     |
| Type of respiratory samples:         |                       |                     |
| Broncho-alveolar lavage              | 9/14 (64.3)           | 25/29 (86.2)        |
| Endotracheal aspirate                | 7/14 (50.0)           | 5/29 (17.2)         |
| Protected specimen brush             | 0/14 (0.0)            | 5/29 (17.2)         |
| Galactomannan index ≥ 1              | 4/5 (80.0)            | 12/17 (70.6)        |
|Galactomannan index                 | 3/9 (2.5 to 5.6)      | 2.1 (0.9 to 5.8)    |
| Positive Aspergillus PCR             | 9/12 (75.0)           | 11/15 (73.3)        |
| Mycological culture                  | 14/14 (100.0)         | 29/29 (100.0)       |
| **Identified species**               |                       |                     |
| Aspergillus fumigatus                | 10/14 (71.4)          | 24/27 (88.9)        |
| Aspergillus niger                    | 0/14 (0.0)            | 1/27 (3.7)          |
| Aspergillus flavus                   | 0/14 (0.0)            | 1/27 (3.7)          |
| Aspergillus terreus                  | 1/14 (7.1)            | 1/27 (3.7)          |
| Other species                        | 3/14 (21.4)           | 0/27 (0.0)          |
| **Antifungal treatment against aspergilosis** |               |                     |
| Initiation of antifungal treatment   | 11/14 (78.6)          | 27/29 (93.1)        |
| Time from IPA diagnosis to first treatment | 1 (-1 to 2)          | 0 (0 to 2)          |
| **First antifungal treatment**       |                       |                     |
| Voriconazole                         | 7/11 (63.6)           | 22/27 (81.5)        |
| Isavuconazole                        | 1/11 (9.1)            | 0/27 (0.0)          |
| Caspofungin                          | 2/11 (18.2)           | 2/27 (7.4)          |
| Anidulafungin                        | 0/11 (0.0)            | 1/27 (3.7)          |
| Liposomal Amphotericin B             | 1/11 (9.1)            | 2/27 (7.4)          |
| **Number of treatment lines used**   |                       |                     |
| 1                                    | 7/14 (50.0)           | 17/29 (58.6)        |
| 2                                    | 3/14 (21.4)           | 7/29 (24.1)         |
| 3                                    | 1/14 (7.1)            | 3/29 (10.3)         |
pulmonary lesions associated with these viruses are different [26, 27]. This suggests that the lower incidence of IPA in COVID-19 patients might be specifically related to SARS-CoV-2 infection.

Impact of invasive pulmonary aspergillosis on outcomes
In the whole study population, combining COVID-19 and influenza patients, IPA was significantly associated with increased 28-day mortality and ICU length of stay. However, the relationship between IPA and duration of mechanical ventilation did not reach significance. In subgroup analyses, IPA was associated with increased duration of mechanical ventilation and ICU length of stay in influenza, but not in COVID-19 patients. Our study is probably underpowered to determine the relationship between IPA and outcomes, or the relationship between antifungal treatment and outcomes. However, previous studies have shown a negative impact on outcome in IAPA and CAPA patients [7, 12].

Strengths and limitations
To the best of our knowledge, our study is the first large multicenter cohort to compare the incidence of IPA between COVID-19 and influenza patients. Further, competing risk analysis, and cause-specific Cox models were used to adjust for potential confounders. However, several limitations should be acknowledged. First, the study was retrospective and there was no systematic screening for IPA, which might have underestimated the overall IPA incidence. Nevertheless, physicians prospectively identified IPA, based on clinical suspicion; and a recent taskforce recommended against routine screening for IPA in critically ill patients [23]. Second, no information was available on bronchoscopy macroscopic data, which may have also led to underestimating the incidence of IPA, because Aspergillus tracheobronchitis could not be diagnosed. Third, no information could be provided on galactomannan in some study patients, which might have also reduced the incidence of probable IPA. Fourth, the evaluation of the two diseases was not done simultaneously because of the absence of influenza during COVID-19 pandemic. Fifth, this study was conducted in Europe, mostly in France, and the results may not be generalizable to other parts of the world. Finally, we chose to use Blot definition for putative IPA, because this definition was validated using histological data in a large international study. However, galactomannan is not considered by this definition and some patients could have IPA with no Aspergillus identified in respiratory specimen. This might have also resulted in underestimating the overall incidence of IPA. However, Verweij definition was also used as a secondary outcome and although the overall IPA incidence was slightly higher in the two groups, IPA incidence was still significantly lower in COVID-19 than in influenza patients.

Conclusions
Overall, the incidence of IPA was low in study patients. Further, putative IPA incidence was lower in SARS-CoV-2 pneumonia than in influenza pneumonia patients. Our study was performed at the beginning of COVID-19 pandemic, it would be interesting to determine how IPA incidence has evolved, especially with routine use of corticosteroids in COVID-19 patients. Screening for IPA should be performed, based on recent recommendations, in patients with clinical deterioration or absence of improvement.

Table 4 (continued)

| Value | Description |
|-------|-------------|
| 10    | Missing values (SARS-CoV-2, n = 4; influenza, n = 6); 5 missing values (SARS-CoV-2, n = 2; influenza, n = 3); 20 missing values (SARS-CoV-2, n = 5; influenza, n = 10); 15 missing values (SARS-CoV-2, n = 4; influenza, n = 11); 22 missing values (SARS-CoV-2, n = 5; influenza, n = 17); 5 missing values (SARS-CoV-2, n = 3; influenza, n = 2) |

Respiratory worsening is defined by significant PaO2/FiO2 ratio deterioration within 72 h of IPA diagnosis. New or increased fever is defined within 72 h of IPA diagnosis. All patients were intubated on the day of IPA diagnosis. More than on respiratory sample may be performed for IPA diagnosis.

ICU, intensive care unit; IPA, invasive pulmonary aspergillosis; PCR, polymerase chain reaction.

Abbreviations
ARDS: Acute respiratory distress syndrome; CAPA: COVID-19-associated IPA; CI: Confidence interval; COPD: Chronic obstructive pulmonary disease; COVID: Coronavirus disease; HR: Hazard ratio; ICU: Intensive care unit; IPA: Invasive pulmonary aspergillosis; IAPA: Influenza-associated IPA; MV: Mechanical ventilation; SAPS II: Simplified acute physiology score II; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; SOFA: Sequential organ failure assessment.

Supplementary Information
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In addition to the authors, the coVAPid study group includes the following collaborators (information to include for individual PubMed record):
Mathilde Bouheneau, CHU de Lille, Centre de Réanimation, F-59000 Lille, France. Boualem Sendid, INSERM U1285, CNRS UMR 8576, Glycobiology in Fungal Pathogenesis and Clinical Applications, Université de Lille ; and Pôle de Biologie-Pathologie-Genétique, Institut de Microbiologie, Service de Parasitologie Mycologie, CHU Lille, F-59000 Lille, France. Sean Boyd, Department of Intensive Care Medicine, Multidisciplinary Intensive Care Research Organization (MICRO), St. James’s Hospital, Dublin, Ireland. Luis Coelho, Polyvalent Intensive Care Unit, Hospital de São Francisco Xavier, CHLO, Lisbon, Portugal. NOVA Medical School, CHRC, New University of Lisbon, Portugal. Julien Maizel,
Service de médecine intensive réanimation, CHU Amiens Picardie, 80000 Amiens, France. Pierre Cuchet, Department of Medical Intensive Care, Caen University Hospital, F-14000 Caen, France. Wafa Zarrougou, Service de réanimation polyvalente, Centre hospitalier de Valenciennes, Valenciennes, France. Deborah Boyer, Medical Intensive Care Unit, Rouen University Hospital, 76000 Rouen, France. Jean-Pierre Quenot, Department of Intensive Care, Francois Mitterrand University Hospital, Dijon, France. Mehdi Imouloudene, Service de réanimation et de soins intensifs, Centre hospitalier de Douai, Douai, France. Marc Pineton de Chambrun, Service de Médecine Intensive Réanimation, Institut de Cardiologie, Groupe Hospitalier Pitié-Salpêtrière, Assistance Publique – Hôpitaux de Paris, Paris Cedex 13, France. Thierry Van Der Linden, Service de médecine intensive réanimation, Hôpital Saint Philibert GHICL, Université catholique, Lille, France. François Arrive, CHU de Poitiers, Médecine Intensive Réanimation, CIC 1402 ALIVE, Université de Poitiers, Poitiers, France. Sebastian Voicu, Department of Medical and Toxicological Critical Care, Lariboisière Hospital, INSERM UMR5-1144, Paris University, Paris, France. Elie Azouly, Service de médecine intensive réanimation, Hôpital Saint-Louis, 75010 Paris, France. Edgard Moglia, Critical Care Department, Hospital Universitari Parc Tauli, Sabadell, Spain Frédéric Pene, Medical Intensive Care Unit, Cochin Hospital, Assistance Publique – Hôpitaux de Paris, Paris, France. Catta Collon, Department of Pulmonology, Hospital Clinic of Barcelona, University of Barcelona, IDIBAPS, CIBERES, Barcelona, Spain. Didier Thevenin, Service de réanimation polyvalente, Centre Hospitalier de Lens, Lens, France. Charlotte Larnat, Service de Médecine Intensive Réanimation, CHU de Tours, Hôpital Bretonneau, 37044 Tours Cedex 9, France. Laurent Argaud, Service de Médecine Intensive – Réanimation, Hôpital Edouard Herriot, Hospices Civils de Lyon, 69437 Lyon Cedex 03, France. Bertrand Guidet, Service de Médecine Intensive Réanimation, Hôpital Saint-Antoine, Assistance Publique-Hôpitaux de Paris, 75012 Paris, France. Matthieu Turpin, Sorbonne Université, Assistance Publique-Hôpitaux de Paris, Service de Médecine Intensive Réanimation, Hôpital Tenon, Paris, France. Damien Contou, Service de réanimation polyvalente, CH-Victor Dupouy, Argenteuil, France. Alexandra Beurton, Service de Médecine Intensive-Réanimation et Pneumologie, Assistance Publique-Hôpitaux de Paris, Hôpital Pitié Salpêtrière, France. Julien Demiselle, Département de Médecine Intensive Réanimation, CHU d'Angers, 49933 Angers Cedex 9, France. David Meguerditchian, Service de médecine intensive réanimation, CHU de Bordeaux, F-33000 Bordeaux, France. Keyvan Razavi, Assistance Publique-Hôpitaux de Paris, Hôpitaux Universitaires Henri-Mondor, Service de Médecine Intensive Réanimation, Université Paris Est Créteil, CARMAS ; INSERM U955, Institut Mondor de recherche Biomédicale, F-94010 Créteil, France. Vasiliki Tsolaki, Intensive Care Unit, University Hospital of Larissa, University of Thessaly, Biopolis Larissa, 41110 Greece. Mehdi Marzouk, Intensive Care Unit, Hôpital de Béthune, 62408 Béthune, France. Guillaume Bruni, Service de réanimation, Hôpital Duchenne, 62200 Boulogne-sur-Mer, France. Nicolas Weiss, Sorbonne Université, Assistance Publique-Hôpitaux de Paris, Sorbonne Université, Hôpital de la Pitié-Salpêtrière, Département de Neurologie, Unité de Médecine Intensive Réanimation Neurologique, Paris, France. Luis Morales, Intensive Care Unit, Hospital Universitari Sagrat Cor, Barcelona, Spain.

Authors' contributions
AR, EL, IML, PP, AD, JL, and SN conceptualized and designed the study. All authors acquired the data, drafted or critically revised the manuscript for important intellectual content, and gave final approval of the submitted version. AR, EL, IML, PP, RN, AT, AD, JL, and SN analyzed and interpreted the data. SN was guarantor of the paper. All authors read and approved the final manuscript.

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Availability of data and materials
All data needed to evaluate the conclusions in this article are present and tabulated in the main text or the appendix. This article is the result of an original retrospective cohort. For individual de-identified raw data that underlie the results reported in this article, please contact the corresponding author.

Declarations

Ethics approval and consent to participate
The Ethics Committee and Institutional Review Boards approved the study protocol (Comité de Protection des Personnes Ouest VI; approved by April 14, 2020; registration number RIPH:20.04.09.60039) as minimal-risk research using data collected for routine clinical practice and waived the requirement for informed consent.

Consent for publication
Not applicable.

Competing interests
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Author details
1CHU de Lille, Médecine Intensive-Réanimation, 59000 Lille, France. 2INSERM U1285, CNRS, UMR 8576 – UGFS – Unité de Glycobiologie Structurale et Fonctionnelle, Université de Lille, 59000 Lille, France. 3Department of Intensive Care Medicine, Multidisciplinary Intensive Care Research Organization (MICRO), St. James’s Hospital, Dublin, Ireland. 4Department of Clinical medicine, School of Medicine, Trinity College Dublin, Dublin, Ireland. 5Hospital Clinic, IDIBAPS, Universidade de Barcelona, Ciberes, Barcelona, Spain. 6Polyvalent Intensive Care Unit, Hospital de São Francisco Xavier, CHLO, Lisbon, Portugal. 7NOVA Medical School, CHRC, New University of Lisbon, Lisbon, Portugal. 8Center for Clinical Epidemiology and Research Unit of Clinical Epidemiology, OHU Odense University Hospital, Odense, Denmark. 9Critical Care Department, Hospital Universitari Parc Taulí, Sabadell, Departament de Medicina, Universitat Autonoma de Barcelona, Barcelona, Spain. 10Service de médecine intensive réanimation, CHU Amiens Picardie, 80000 Amiens, France. 11Department of Pulmonology, Hospital Clinic of Barcelona, IDIBAPS, CIBERES, Universitat de Barcelona, Barcelona, Spain. 12Department of Medical Intensive Care, Caen University Hospital, 14000 Caen, France. 13Service de réanimation polyvalente, Centre hospitalier de Valenciennes, Valenciennes, France. 14Medical Intensive Care Unit, UNIROUEN, INSERM U1096, FRU-REMOD-VHF, Rouen University Hospital, 76000 Rouen, France. 15Department of Intensive Care, François Mitterrand University Hospital, Dijon, France. 16Service de réanimation et de soins intensifs, Centre hospitalier de Douai, Douai, France. 17Service de Médecine Intensive Réanimation, Institut de Cardiologie, Groupe Hospitalier Pitié-Salpêtrière, Assistance Publique – Hôpitaux de Paris, Paris Cedex 13, France. 18Service de réanimation, Centre hospitalier de Roubaix, Roubaix, France. 19Service de médecine intensive réanimation, Hôpital Saint Philibert GHICL, Université catholique, Lille, France. 20CHU de Poitiers, Médecine Intensive Réanimation, CIC 1402 ALIVE, Université de Poitiers, Poitiers, France. 21Department of Medical and Toxicological Critical Care, Lariboisière Hospital, INSERM UMR5-1144, Paris University, Paris, France. 22Service de médecine intensive réanimation, Hôpital Saint-Louis, 75010 Paris, France. 23First Department of Critical-Care Medicine, Medical School, Evangelismos Hospital, National and Kapodistrian University of Athens, Athens, Greece. 24Medical Intensive Care Unit, Cochin Hospital, Assistance Publique – Hôpitaux de Paris, Paris, France. 25First Department of Pulmonary Medicine and Intensive Care Unit, Sotiria Chest Hospital, National and Kapodistrian University of Athens, Athens, Greece. 26Service de réanimation polyvalente, Centre Hospitalier de Lens, Lens, France. 27Service de Médecine Intensive Réanimation, CHU de Nantes, Nantes, France. 28Service de Médecine Intensive Réanimation, CHU de Tours, Hôpital Bretonneau, 37044 Tours Cedex 9, France.
References

1. Delsuc C, Cottereau A, Fréalle E, Bienvenu A-L, Desseín R, Jarraud L, et al. Putative invasive pulmonary aspergillosis in critically ill patients with chronic obstructive pulmonary disease: a matched cohort study. Crit Care. 2015;19.

2. Contou D, Dorison M, Rosman J, Schlemmer F, Gibelin A, Foulet F, et al. Aspergillus-positive lower respiratory tract samples in patients with the acute respiratory distress syndrome: a 10-year retrospective study. Ann Intensive Care. 2016;6:52.

3. Levesque E, Att-Annar M, Ducad M, Clavie R, Fera C, Foulet F, et al. Invasive pulmonary aspergillosis in cirrhotic patients: analysis of a 10-year clinical experience. Ann Intensive Care. 2019;9:31.

4. Gustot T, Maillard E, Bocci M, Surin R, Télo P, Degré D, et al. Invasive aspergillosis in patients with severe alcoholic hepatitis. J Hepatol. 2014;60:267–74.

5. Pardo E, Lemiale V, Mokart D, Stocin A, Moreau A-S, Kerhuel L, et al. Invasive pulmonary aspergillosis in critically ill patients with hematological malignancies. Intensive Care Med. 2019;45:1732–41.

6. Taccone FS, Van den Abeele A-M, Bulpa P, Misset B, Meersseman W, Cardoso T, et al. Epidemiology of invasive aspergillosis in critically ill patients: clinical presentation, underlying conditions, and outcomes. Crit Care. 2015;19:7.

7. Schauwvlieghe AFAD, Rijnders BJ, Philips N, Verwijs R, Vanderbeke L, Van Tienen C, et al. Invasive aspergillosis in patients admitted to the intensive care unit with severe influenza: a retrospective cohort study. Lancet Respir Med. 2018;6:782–92.

8. Koehler P, Bassetti M, Chakraborti A, Chen SCA, Colombo AL, Hoehnig M, et al. Defining and managing COVID-19-associated pulmonary aspergillosis: the 2020 EOMM/ISHAM consensus criteria for research and clinical guidance. Lancet Infect Dis. 2021;21:e149–62.

9. Dellière S, Dudaogon E, Fodil S, Voicu S, Collet M, Ollic P-A, et al. Risk factors associated with COVID-19-associated pulmonary aspergillosis in ICU patients: a French multicentric retrospective cohort. Clin Microbiol Infect. 2020;26:3316401.

10. Fekkar A, Lampros A, Mayaux J, Poignon C, DeMERET S, Constantin J-M, et al. Occurrence of invasive pulmonary fungal infections in patients with severe COVID-19 admitted to the ICU. Am J Resp Care Med. 2021;203:307–17. https://doi.org/10.1164/rcrn.cc20009-34000C.

11. Prates T, Wauters J, Giacono DR, Salmant-Garcia J, Maertens J, Bourgeois M, et al. Risk factors and outcome of pulmonary aspergillosis in critically ill coronavirus disease 2019 patients: a multinational observational study by the European Confederation of Medical Mycology. Clin Microbiol Infect. 2021. http://www.ncbi.nlm.nih.gov/pubmed/34454093.
12. Prattes J, Wauters J, Giacobbe DR, Lagrou K, Hoenigl M, ECMM ‑ CAPA Study Group. Diagnosis and treatment of COVID‑19 associated pulmonary aspergillosis in critically ill patients: results from a European confederation of medical mycology registry. Intensive Care Med. 2021. http://www.ncbi.nlm.nih.gov/pubmed/34269853

13. Bartoletti M, Pascale R, Cricca M, Rinaldi M, Maccaro A, Bussini L, et al. Epidemiology of invasive pulmonary aspergillosis among COVID‑19 intubated patients: a prospective study. Clin Infect Dis. 2020. http://www.ncbi.nlm.nih.gov/pubmed/32719848

14. Permpalung N, Chiang TP‑Y, Massie AB, Zhang SX, Avery RK, Nematol‑lahi S, et al. COVID‑19‑associated pulmonary aspergillosis in mechanically ventilated patients. Clin Infect Dis. 2021. http://www.ncbi.nlm.nih.gov/pubmed/33693551

15. Salmanton‑Garcia J, Sprute R, Stemler J, Bartoletti M, Dupont D, Valerio M, et al. COVID‑19‑associated pulmonary aspergillosis, March‑August 2020. Emerg Infect Dis. 2021;27:1077–86.

16. Gangneuxjp, Dannaoui E FA. Fungal infections in mechanically ventilated COVID‑19 patients in the ICU during the 1st wave: the French multicenter MYCOVID study. Lancet Respir Med. 2021 (in press).

17. Janssen NAF, Nyga R, Vanderbeke L, Jacobs C, Ergün M, Buij JB, et al. Multinational observational cohort study of COVID‑19‑associated pulmonary aspergillosis I. Emerg Infect Dis. 2021;27:2892–8.

18. Razazi K, Arrestier R, Haudebourg AF, Benelli B, Canteaux G, Decousser J, et al. Risks of ventilator‑associated pneumonia and invasive pulmonary aspergillosis in patients with viral acute respiratory distress syndrome related or not to Coronavirus 19 disease. Crit Care [Internet]. BioMed Central, 2020 [cited 2021 Jan 22];24:699. https://ccforum.biomedcentral.com/articles/doi.org/10.1186/s13054-020-03417-0

19. Verweij PE, Rijnders BJA, Brüggemann RIM, Azoulay E, Bassetti M, Blot S, et al. Review of influenza‑associated pulmonary aspergillosis in ICU patients and proposal for a case definition: an expert opinion. Intensive Care Med. 2020;46:1524–35.

20. Rouzé A, Martin‑Loeches I, Povoa P, Makris D, Artigas A, Bouchereau M, et al. Relationship between SARS‑CoV‑2 infection and the incidence of ventilator‑associated lower respiratory tract infections: a European multicenter cohort study. Intensive Care Med. 2021. http://www.ncbi.nlm.nih.gov/pubmed/33388794

21. Blot SJ, Taccone FS, Van den Abeele A‑M, Balpa P, Meersseman W, Brusselaers N, et al. A clinical algorithm to diagnose invasive pulmonary aspergillosis in critically ill patients. Am J Respir Crit Care Med. 2012;186:56–64.

22. Prentice RL, Kalbfleisch JD, Peterson AV, Flournoy N, Farewell VT, Breslow NE. The analysis of failure times in the presence of competing risks: Biometrics. 1978;34:541–54.

23. Verweij PE, Brüggemann RIM, Azoulay E, Bassetti M, Blot S, Buij JB, et al. Taskforce report on the diagnosis and clinical management of COVID‑19 associated pulmonary aspergillosis. Intensive Care Med. 2021;47:819–34.

24. Therneau T‑M, Grambsch P‑M. Modeling survival data: extending the cox model. New‑York (2000).

25. Coste A, Frérou A, Raute A, Coutraud F, Morin J, Egretoue P‑Y, et al. The extent of aspergillosis in critically ill patients with severe influenza pneumonia: a multicenter cohort study. Crit Care Med. 2021;49:934–42.

26. van de Veerdonk FL, Brüggemann RIM, Vos S, De Hertogh G, Wauters J, Reijers MHE, et al. COVID‑19‑associated Aspergillus tracheobronchitis: the interplay between viral tropism, host defence, and fungal invasion. Lancet Respir Med. 2021;9:795–802.

27. Ackermann M, Verleden SE, Kuehnel M, Haverich A, Weite T, Laenger F, et al. Pulmonary vascular endothelitis, thrombosis, and angiogenesis in Covid‑19. N Engl J Med. 2020;383:120–8.

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