

Multinational Observational Cohort Study of COVID-19–Associated Pulmonary Aspergillosis¹

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We performed an observational study to investigate intensive care unit incidence, risk factors, and outcomes of coronavirus disease–associated pulmonary aspergillosis (CAPA). We found 10%–15% CAPA incidence among 823 patients in 2 cohorts. Several factors were independently associated with CAPA in 1 cohort and mortality rates were 43%–52%.

Incidence of coronavirus disease (COVID-19)–associated pulmonary aspergillosis (CAPA) in hospital intensive care units (ICUs) is 3.8%–33.3% (1–9). Variations might be explained by differences in patient populations and CAPA definitions used, complicating direct comparisons between studies.

Diagnosing CAPA is complex because cases frequently lack typical radiologic features and European Organization for Research and Treatment of Cancer and the Mycoses Study Group Education and Research Consortium (EORTC/MSGERC) host factors (10) and because mycologic evidence is difficult to obtain. Serum galactomannan (GM) detection has low sensitivity in CAPA (7,10).

The European Confederation of Medical Mycology and International Society for Human and Animal Mycology (ECMM/ISHAM) published consensus criteria for a CAPA definition (11). We used these criteria to perform an observational cohort study to assess CAPA incidence in patients with COVID-19 admitted to ICUs during the first wave of the COVID-19 pandemic.

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The Study

We collected partially prospective and partially retrospective data for 823 patients in 2 cohorts. The discovery cohort comprised patients with PCR-confirmed or clinically presumed COVID-19 admitted to 4 ICUs in the Netherlands and 4 ICUs in Belgium during February 28–May 27, 2020. The validation cohort comprised patients with PCR-confirmed COVID-19 admitted because of respiratory insufficiency to 3 participating ICUs in France during April 7–May 31, 2020 (Appendix Methods, Table 1, <https://wwwnc.cdc.gov/EID/article/27/11/21-1174-App1.pdf>).

¹The results of this study were presented at the Scientific Spring Meeting of the Dutch Society of Medical Microbiology (NVMM) and the Royal Dutch Society of Microbiology (KNVM), held online March 30–31, 2021; and at the 31st European Congress of Clinical Microbiology & Infectious Diseases (ECCMID), held online from July 9–12, 2021.

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Table 1. Demographic, clinical, and mycologic characteristics of the discovery cohort in a multinational observational study of COVID-19–associated pulmonary aspergillosis in 3 countries in Europe, 2020*

| Characteristics | Total population, n = 519 | CAPA, n = 42 | CAPA excluded, n = 237 | p value |
|--|---------------------------|--------------------------|---------------------------|------------------|
| Age, y | 64 (55–72) | 68 (61–73) | 65 (57–71) | 0.12 |
| Sex | | | | |
| F | 141 (27) | 8 (19) | 58 (24) | |
| M | 378 (73) | 34 (81) | 179 (76) | 0.56 |
| BMI, kg/m ² | 27.2 (24.4–31.0); n = 507 | 27.4 (23.6–30.2); n = 40 | 26.9 (24.4–30.9); n = 231 | 0.72 |
| Underlying conditions | | | | |
| Cardiovascular disease† | 291 (56) | 25 (60) | 130 (55) | 0.62 |
| Diabetes mellitus | 139 (27) | 9 (21) | 61 (26) | 0.70 |
| Asthma | 37 (7) | 1 (2) | 19 (8) | 0.33 |
| COPD | 44 (9) | 8 (19) | 19 (8) | 0.042 |
| Liver cirrhosis | 6 (1) | 0 | 2 (0.8) | 1.00 |
| Rheumatological disease | 31 (6) | 5 (12) | 14 (6) | 0.18 |
| HIV/AIDS | 6 (1) | 3 (7) | 1 (0.4) | 0.011 |
| Solid organ malignancy | 28 (5) | 3 (7) | 11 (5) | 0.45 |
| EORTC/MSGERC host factors | | | | |
| Any‡ | 70 (16); n = 426 | 13 (33); n = 39 | 31 (19); n = 166 | 0.053 |
| Recent neutropenia§ | 7 (2); n = 413 | 1 (3); n = 38 | 5 (3); n = 156 | 1.00 |
| Hematologic malignancy | 18 (4) | 4 (10) | 9 (4) | 0.11 |
| Receipt of allogeneic SCT | 4 (0.8); n = 516 | 0 | 3 (1); n = 236 | 1.00 |
| Receipt of SOT | 6 (1) | 1 (2) | 2 (0.8) | 0.39 |
| Systemic corticosteroids ≤30 d before ICU admission, any dose | 38 (9); n = 430 | 7 (18); n = 39 | 14 (9); n = 160 | 0.14 |
| T or B cell immunosuppressants other than corticosteroids ≤90 d before ICU admission | 31 (6); n = 514 | 7 (17) | 12 (5); n = 233 | 0.014 |
| Inherited severe immunodeficiency | 0; n = 517 | 0 | 0; n = 236 | NA |
| ICU treatment data | | | | |
| Invasive mechanical ventilation | 423 (82); n = 517 | 40 (98); n = 41 | 225 (95) | 0.70 |
| No. invasive ventilation days¶ | 14 (9–24); n = 395 | 16 (13–27); n = 37 | 18 (11–30); n = 212 | 0.98 |
| RRT during ICU admission | 93 (18); n = 516 | 17 (41) | 44 (19); n = 236 | 0.004 |
| Systemic corticosteroids during ICU admission | 216 (42); n = 516 | 20 (48) | 131 (56); n = 236 | 0.40 |
| Outcome data | | | | |
| ICU death | 154 (30); n = 518 | 22 (52) | 81 (34) | 0.036 |
| ICU LOS, d# | 14 (8–24); n = 491 | 18 (12–27); n = 39 | 20 (12–32); n = 222 | 0.84 |
| Mycologic diagnostic tests | | | | |
| Serum GM OD >0.5, no. positive (%); no. values reported/no. performed | 3 (2); 134/176 | 3 (11); 28/28 | 0; 106/148 | NA |
| Serum GM OD** | 0.10 (0.10–0.10); n = 134 | 0.10 (0.06–0.14); n = 28 | 0.10 (0.10–0.10); n = 106 | 0.95 |
| Positive BALF/BL culture | 17 (10); n = 166 | 17 (42); n = 41 | 0; n = 125 | NA |
| BALF/BL GM OD ≥1.0, no. positive (%); no. OD values reported/no. BL/BALF performed | 32 (19); 90/166 | 32 (78); 34/41 | 0; 55/125 | NA |
| BALF/BL GM OD** | 0.20 (0.10–1.50); n = 90 | 1.80 (1.00–3.90); n = 35 | 0.10 (0.10–0.20); n = 55 | <0.001 |
| Positive BALF/BL PCR, any C _t , no. positive (%); no. reported/no. tested | 9 (5); 11/166 | 7 (17); 7/41 | 2 (2); 4/125†† | NA |
| Days between ICU admission and first positive mycologic test‡‡ | NA | 6 (3–9); n = 41 | NA | NA |

*Data are presented as no. (%) or median (IQR) unless otherwise indicated. Continuous variables were compared by Mann-Whitney U test, categorical variables by Fisher exact test with omission of missing data, unless stated otherwise. Total percentages might not equal 100% because of rounding. Bold text indicates statistical significance. BAL, bronchoalveolar lavage; BALF, BAL fluid; BL, bronchial lavage; BMI, body mass index; CAPA, COVID-19–associated pulmonary aspergillosis; COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease; C_t, cycle threshold; CT, computed tomography; ECMO, extracorporeal membrane oxygenation; EORTC/MSGERC, European Organization for Research and Treatment of Cancer and the Mycoses Study Group Education and Research Consortium; GM, galactomannan; ICU, intensive care unit; IQR, interquartile range; LOS, length of stay; NA, not applicable; NBL, nonbronchoscopic lavage; OD, optical density; RRT, renal replacement therapy; SCT, stem cell transplantation; SOT, solid organ transplant.

†Includes hypertension

‡Includes any use of systemic corticosteroids before ICU admission; If data on one or more EORTC host factors were missing, then data were regarded as missing for this variable.

§Neutropenia includes absolute neutrophil count of <0.5 × 10⁹ cells/L for >10 d.

¶If transferred to another hospital from ICU and still on ventilatory support of any kind, duration of invasive mechanical ventilatory support was regarded as missing data and not included in the analyses. The same holds true for those who received a tracheostomy for a prolonged weaning trajectory.

#Data on ICU LOS were regarded as missing if transfer to another hospital was the reason for ICU discharge because exact ICU LOS was unknown.

**When multiple values were reported for 1 patient, the median of these values was used for further calculations.

††Positive PCR with C_t values ≥36 as only positive mycologic criterion.

‡‡Mycologic test considered a criterion for proven, probable, or possible CAPA according to the 2020 European Confederation for Medical Mycology/International Society for Human and Animal Mycology classification (11).

We applied ECMM/ISHAM classification criteria for CAPA (11). We considered bronchial lavage (BL) equivalent to bronchoalveolar lavage (BAL). We assumed all CAPA classified patients demonstrated clinical factors and radiographic abnormalities. We defined 3 patient groups: CAPA, CAPA-excluded, and CAPA not classifiable (Figure 1; Appendix).

We included 519 patients in the discovery cohort; median age was 64 years, 73% were male, and 82% required invasive mechanical ventilation during ICU admission (Table 1; Appendix Table 2, 3, 4). Among patients in the discovery cohort, 279 (54%) were classifiable: 6 (2%) as CAPA proven, 32 (12%) as probable CAPA, and 4 (1%) as possible CAPA (Figure 1, panel A; Appendix Results, Tables 5, 6). CAPA incidence among classifiable patients was 15% (42/279); 85% were CAPA-excluded. Among patients in the discovery cohort, 46% (240/519) were not classifiable, including 3 who did not fulfill the criteria for possible CAPA (Figure 1, panel A). In patients with any EORTC/MSGERC host factor, CAPA incidence was 30% (13/44), compared with 16% (26/161) in patients with no host factors ($p = 0.053$).

Chronic obstructive pulmonary disease (COPD; $p = 0.04$) and HIV/AIDS ($p = 0.01$) were more

prevalent in CAPA patients (Table 1; Appendix Table 2). Among CAPA patients, 33% had ≥ 1 EORTC/MSGERC host factor, compared with 19% of CAPA-excluded patients ($p = 0.053$). Corticosteroid use was not more prevalent in the CAPA group ($p = 0.14$), in contrast to other immunosuppressant drugs ($p = 0.01$). In logistic regression analysis, corticosteroid use at any dose before or during ICU admission was not independently associated with CAPA development. However, COPD, HIV/AIDS, and use of other immunosuppressant drugs before ICU admission were associated with CAPA (Appendix Figure 1, panel A).

Among CAPA patients who underwent BAL or BL, *Aspergillus* culture was positive in 42%, GM was positive (optical density [OD] ≥ 1.0) in 78%, and *Aspergillus* PCR was positive in 17%. Among CAPA patients who underwent nonbronchoscopic lavage, 67% had positive cultures. Serum GM was positive in 11% of tested CAPA patients. Median time between ICU admission and first positive mycologic test was 6 (interquartile range [IQR] 3–9) days (Table 1; Appendix Table 7).

The proportion of patients receiving systematic corticosteroid treatment in ICUs was not

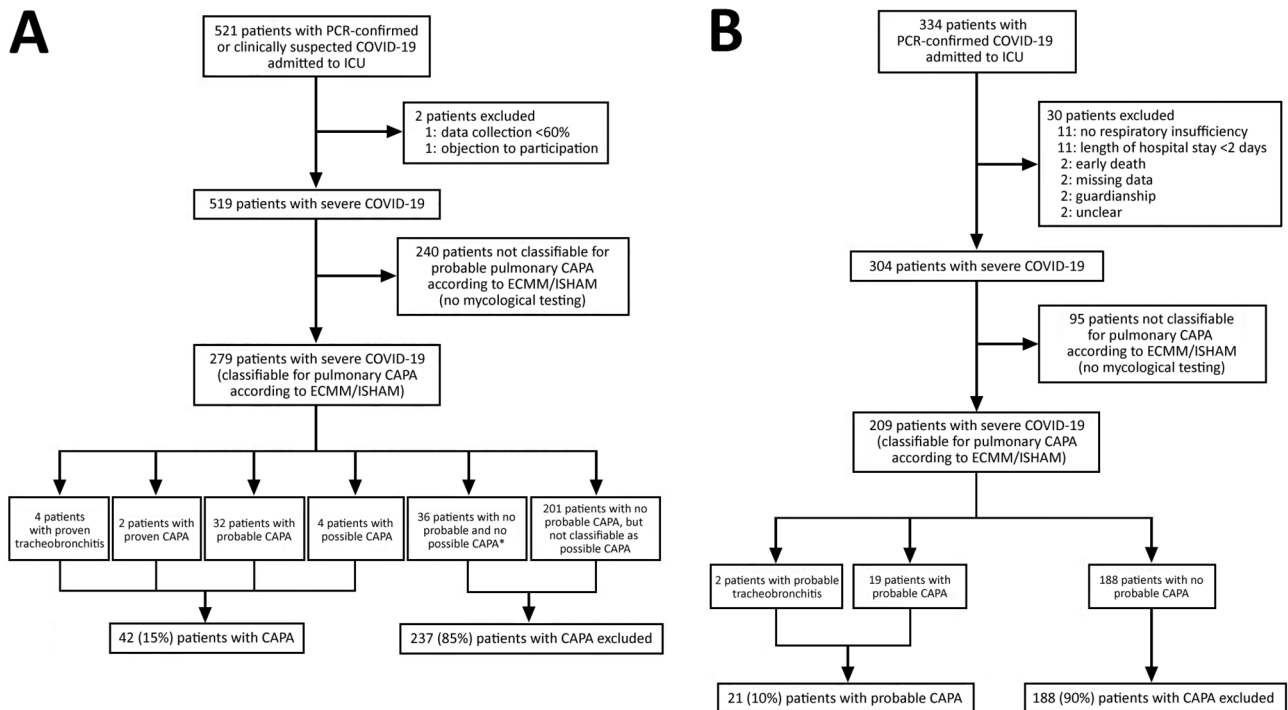


Figure 1. Flowchart of the study inclusion process for a multinational observational study of CAPA in 3 countries in Europe, 2020.

A) Discovery cohort; B) validation cohort. For further analyses, patients with proven, probable, and possible CAPA were designated to the CAPA group. Patients were classified to the CAPA excluded group when they had ≥ 1 negative mycological test according to 2020 ECMM/ISHAM classification consensus criteria (11). Patients who did not undergo any of the mycological tests were designated to the CAPA not classifiable group. *Value includes 6 patients in whom CAPA was excluded at the time of autopsy. CAPA, COVID-19–associated pulmonary aspergillosis; COVID-19, coronavirus disease; ECMM/ISHAM, European Confederation for Medical Mycology/International Society for Human and Animal Mycology; ICU, intensive care unit.

significantly different between CAPA and CAPA-excluded groups ($p = 0.40$), nor was corticosteroid dose ($p = 0.88$) (Table 1; Appendix Table 4). Antifungal treatment was administered to 16% (83/519) of patients, 88% of CAPA patients, and 15% of CAPA-excluded patients (Appendix Table 8). ICU mortality rates were significantly higher in CAPA patients (52%) than in CAPA-excluded patients (34%) ($p = 0.04$; Table 1; Appendix Table 4); mortality rates were 67% for patients with positive serum GM. CAPA patients demonstrated reduced survival ($p = 0.02$) (Figure 2, panel A); estimated median survival was 42 days after ICU admission. When correcting for covariates, CAPA was not independently associated with ICU mortality rates, but older age and acute kidney injury (AKI) during ICU stay were (Appendix Figure 1, panel B).

We included 304 patients in the validation cohort (Figure 1, panel B); median age was 63 years, 25% were male, and 76% required invasive mechanical ventilation (Table 2; Appendix Tables 9, 10). Ultimately, 209/304 (69%) patients were classifiable for CAPA: 21 (10%) probable CAPA and 188 (90%) CAPA excluded (Figure 1, panel B; Appendix Results, Tables 5, 11). Among patients with EORTC/MSGERC host factors, CAPA incidence was 13% (3/23), compared with 10% (18/186) among patients without host factors ($p = 0.71$).

All 21 probable CAPA patients were female; cardiovascular disease, excluding hypertension ($p = 0.02$), and bronchiectasis ($p = 0.03$) were more prevalent in this group (Table 2; Appendix Table 9). Use of corticosteroids before or during ICU admission or other immunosuppressant drugs before ICU admission were not independently associated with CAPA (Appendix Figure 1, panel C). In the validation cohort, 19% received antifungal treatment;

57% of the CAPA group received antifungal treatment (Appendix Table 8).

Corticosteroid use during ICU stay was not significantly different between the CAPA and CAPA-excluded groups ($p = 0.82$) in the validation cohort. ICU mortality rates were higher in the CAPA group than the CAPA-excluded group (43% vs. 25%; $p = 0.12$) (Table 2; Figure 2, panel B; Appendix Table 10). The ICU mortality rate was 50% in patients with positive serum GM. CAPA was not independently associated with ICU death, but older age and AKI during ICU admission were (Appendix Table 10, Figure 1, panel D).

Conclusions

We found CAPA incidence was 10%–15%, corresponding to the 14%–19% reported in other studies (8,9). Discovery cohort CAPA incidence was similar to influenza-associated pulmonary aspergillosis (IAPA) incidence in ICUs (12,13). CAPA seems to develop later after ICU admission than IAPA. Median time to first positive mycologic test in our study was 6 days after ICU admission, similar to other studies reporting 4–8 days (7–9) but in contrast to the median 3 days reported for IAPA (12,14).

Corticosteroids were not associated with CAPA in our study, consistent with previous reports (7–9), but contrasting associations seen with invasive pulmonary aspergillosis (IPA) and IAPA (12). This finding might be explained by possible dual effects of corticosteroids in COVID-19, impairing anti-*Aspergillus* immunity while simultaneously ameliorating the hyperinflammatory immune dysregulation and associated tissue damage conducive to IPA.

We found CAPA ICU mortality rates were 43%–52%, in line with previous reports (7–9) and

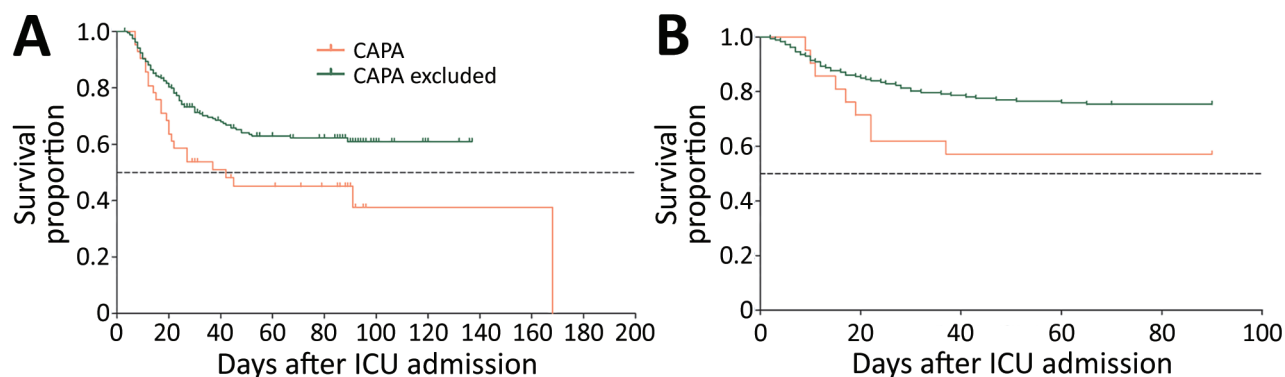


Figure 2. Kaplan-Meier survival curves comparing patients with CAPA and those classified as CAPA excluded in a multinational observational study. A) Discovery cohort; B) validation cohort. Survival analysis performed by using Mantel-Cox log rank test. Survival over time differs significantly in the discovery cohort ($n = 279$); median estimated survival in the CAPA group is 42.0 days ($p = 0.015$ by log rank test). In the validation cohort ($n = 209$), survival over time is not significantly different between the 2 groups ($p = 0.065$ by log rank test). CAPA, COVID-19–associated pulmonary aspergillosis; COVID-19, coronavirus disease; ICU, intensive care unit.

comparable to those for IAPA (12). We could not assess antifungal treatment effects on mortality rates, but CAPA patients in the validation cohort who received antifungal treatment demonstrated a trend toward improved survival (Appendix Figure 2).

Table 2. Demographic, clinical, and mycologic characteristics of the validation cohort in a multinational observational study of COVID-19-associated pulmonary aspergillosis in 3 countries in Europe, 2020*

| Characteristics | Total population, n = 304 | CAPA, n = 21 | CAPA excluded, n = 188 | p value |
|--|-----------------------------|--------------------------|-----------------------------|------------------|
| Age, y | 63 (55–71) | 67 (59–75) | 62 (53–69) | 0.06 |
| Sex | | | | |
| F | 227 (75) | 21 (100) | 141 (75) | |
| M | 77 (25) | 0 | 47 (25) | 0.005 |
| BMI, kg/m ² | 30.0 (26.0–34.4); n = 296 | 30.2 (26.1–32.8); n = 20 | 30.0 (26.4–34.5); n = 185 | 0.84 |
| Underlying conditions | | | | |
| Active hematologic malignancy | 10 (3) | 0 | 6 (3) | 1.00 |
| Cardiovascular disease† | 185 (61) | 17 (81) | 112 (60) | 0.06 |
| Diabetes mellitus | 92 (30) | 9 (43) | 62 (33) | 0.47 |
| Asthma | 22 (7) | 2 (10) | 12 (6) | 0.64 |
| COPD | 20 (7) | 2 (10) | 12 (6) | 0.64 |
| Liver cirrhosis‡ | 5 (2) | 2 (10) | 2 (1) | 0.051 |
| Autoimmune disease | 16 (5) | 2 (10) | 11 (6) | 0.63 |
| HIV/AIDS | 3 (1) | 0 | 1 (0.5) | 1.00 |
| Active solid organ malignancy | 4 (1) | 1 (5) | 3 (2) | 0.35 |
| Bronchiectasis | 5 (2) | 2 (10) | 1 (0.5) | 0.027 |
| EORTC/MSGERC host factors | | | | |
| Any§ | 35 (12) | 3 (14) | 20 (11) | 0.71 |
| Recent neutropenia¶ | 0; n = 303 | 0 | 0; n = 187 | NA |
| Hematological malignancy | 10 (3) | 0 | 6 (3) | 1.00 |
| Receipt of SOT | 9 (3) | 1 (5) | 5 (3) | 0.48 |
| Corticosteroids ≥0.3 mg/kg for ≥3 wks within previous 60 d | 17 (6) | 2 (10) | 10 (5) | 0.34 |
| Other immunosuppressants <90 d before ICU admission | 23 (8) | 2 (10) | 16 (9) | 0.70 |
| ICU treatment data | | | | |
| Invasive mechanical ventilation | 228 (76); n = 302 | 19 (95); n = 20 | 168 (89) | 0.70 |
| No. invasive ventilation days | 15 (9–25); n = 212 | 18 (13–25); n = 17 | 15 (9–25); n = 157 | 0.21 |
| RRT | 64 (21); n = 303 | 11 (55); n = 20 | 47 (25) | 0.008 |
| Systemic corticosteroids during ICU admission | 147 (49); n = 303 | 11 (52) | 106 (57); n = 187 | 0.82 |
| Outcome data | | | | |
| ICU death | 69 (23); n = 299 | 9 (43) | 46 (25); n = 185 | 0.12 |
| ICU LOS, d# | 14 (8–26); n = 295 | 22 (12–35); n = 20 | 18 (10–28); n = 183 | 0.27 |
| Mycologic diagnostic tests | | | | |
| Serum GM OD >0.5 | 4 (2); n = 172** | 4 (22); n = 18 | 0; n = 154†† | NA |
| Serum GM OD | 0.07 (0.04–0.12); n = 172** | 0.10 (0.06–0.34); n = 18 | 0.06 (0.04–0.11); n = 154†† | 0.008 |
| Positive BALF culture | 11 (8); n = 135 | 11 (52) n = 21 | 0; n = 114 | NA |
| BALF GM OD ≥1.0 | 13 (11); n = 123 | 13 (62) n = 21 | 0; n = 102 | NA |
| BALF GM OD‡‡ | 0.12 (0.05–0.32); n = 123 | 1.10 (0.12–3.06); n = 21 | 0.11 (0.05–0.18); n = 102 | <0.001 |
| Positive BALF PCR, any Ct | 8 (13); n = 64 | 8 (53); n = 15 | 0; n = 49 | NA |
| Serum β-D-glucan value ≥80 pg/mL | 37 (20); n = 184 | 8 (42); n = 19 | 29 (18); n = 160 | 0.030 |
| Serum β-D-glucan value§§ | 31 (13–60); n = 184 | 34 (31–156); n = 19 | 31 (10–59); n = 160 | 0.055 |

*Data are presented as no. (%) or median (IQR), unless stated otherwise. Continuous variables were compared by Mann-Whitney U test, categorical variables by Fisher exact test with omission of missing data, unless stated otherwise. Total percentages might not equal 100% because of rounding. Bold text indicates statistical significance. BAL, bronchoalveolar lavage; BALF, BAL fluid; BL, bronchial lavage; BMI, body mass index; CAPA, COVID-19-associated pulmonary aspergillosis; COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease; Ct, cycle threshold; CT, computed tomography; ECMO, extracorporeal membrane oxygenation; EORTC/MSGERC, European Organization for Research and Treatment of Cancer and the Mycoses Study Group Education and Research Consortium; ICU, intensive care unit; IQR, interquartile range; GM, galactomannan; LOS, length of stay; NA, not applicable; OD, optical density; RRT, renal replacement therapy; SAPS, simplified acute physiology score; SOT, solid organ transplant; TBA, tracheobronchial aspirate.

†Includes Factor V Leiden mutation and hypertension.

‡Includes hemochromatosis.

§Includes use of any systemic corticosteroids. We did not assess receipt of an allogeneic stem cell transplant, presence of an inherited severe immunodeficiency, and presence of acute graft-versus-host disease.

¶Neutropenia includes absolute neutrophil count of $<0.5 \times 10^9/L$ for >10 d.

#Data on ICU LOS were regarded as missing if still admitted at the time of data entry or if transfer to another hospital was the reason for ICU discharge.

**Serum GM performed in 173 patients, including 1 patient with an unknown result.

††Serum GM values known for 154 patients, unknown value in 1 patient.

‡‡One value of >6.0 entered as 6.0.

§§One value of >500 pg/mL entered as 500 pg/mL.

The first limitation of our study is that assuming clinical and imaging factors were available for all patients classified with CAPA possibly led to overreporting of CAPA. Excluding CAPA based on 1 negative mycologic test might have led to underreporting. Another limitation was that patients undergoing mycologic workup were likely more severely ill, which becomes apparent when comparing baseline and outcome data of the CAPA not classifiable group to the other 2 groups (Appendix Tables 5–12). Several classifications have been published or updated after we initiated this study; therefore, not all diagnostic modalities were evaluated, and we used some terms, such as BAL and BL, interchangeably (11,15).

In conclusion, we report CAPA incidence of 10%–15% in COVID-19 patients admitted to ICUs, CAPA ICU mortality rates of 43%–52%, and decreased survival over time. Clinicians should be aware of CAPA and that underlying factors, including COPD, immunosuppressant drugs other than corticosteroids, and HIV/AIDS, can increase the risk for CAPA.

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