

## COVID-19 Associated Pulmonary Aspergillosis in Mechanically Ventilated Patients

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### Summary

Aspergillosis occurs at a variable incidence in people with severe COVID-19, depending on diagnostic approach and definitions deployed. Associated poor outcomes may be improved with early detection and antifungal therapy, warranting development of better non-invasive diagnostic and prevention strategies.

## Abstract

**Background:** COVID-19 associated pulmonary aspergillosis (CAPA) occurs in critically ill COVID-19 patients. Risks and outcomes remain poorly understood.

**Methods:** A retrospective cohort study of adult mechanically ventilated COVID-19 patients admitted to five Johns Hopkins hospitals was conducted between March and August 2020. CAPA was defined using composite clinical criteria. Fine and Gray competing risks regression was used to analyze clinical outcomes and multilevel mixed-effects ordinal logistic regression was used to compare longitudinal disease severity scores.

**Results:** Amongst the cohort of 396 people, 39 met criteria for CAPA. Compared to those without, patients with CAPA were more likely to have underlying pulmonary vascular disease (41% vs 21.6%,  $p=0.01$ ), liver disease (35.9% vs 18.2%,  $p=0.02$ ), coagulopathy (51.3% vs 33.1%,  $p=0.03$ ), solid tumors (25.6% vs 10.9%,  $p=0.017$ ), multiple myeloma (5.1% vs 0.3%,  $p=0.027$ ), corticosteroid exposure during index admission (66.7% vs 42.6%,  $p=0.005$ ), and had a lower BMI (median 26.6 vs 29.9,  $p=0.04$ ). People with CAPA had worse outcomes as measured by ordinal severity of disease scores, requiring longer time to improvement (adjusted odds ratio 1.09, 95% CI 1.08-1.11,  $p<0.001$ ), and advancing in severity almost twice as fast (subhazard ratio, sHR 1.8, 95% CI 1.3-2.5,  $p<0.001$ ). People with CAPA were intubated twice as long as those without (sHR 2.0, 95% CI 1.4-2.8,  $p<0.001$ ) and had a longer hospital length of stay [median (IQR) 41.1 (20.5, 72.4) vs 18.5 (10.7, 31.8),  $p<0.001$ ].

**Conclusion:** CAPA is associated with poor outcomes. Attention towards preventative measures (screening and/or prophylaxis) is warranted in people with high risk of developing CAPA.

Keywords: Aspergillosis; CAPA; COVID-19; SARS-CoV-2

## Introduction

As of November 2020, the pandemic of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)- associated coronavirus disease 2019 (COVID-19) has infected over 50 million patients and resulted in over 1.25 million deaths worldwide. Approximately 15-30% of infections are severe, requiring oxygen support, and 5-15% are critically ill, requiring mechanical ventilation in intensive care units (ICU).[1–3] With severe pulmonary inflammation, compromised pulmonary defenses, ventilator dependence, and receipt of immunosuppressive drugs, patients with severe COVID-19 are at risk for secondary infections. Recent studies have drawn attention to high rates of COVID-19 associated pulmonary aspergillosis (CAPA), with reports from Europe estimating prevalence of 5-30% in patients with severe COVID-19.[4–11]

European investigators have proposed case definitions for “probable” CAPA which includes positive galactomannan (GM) in serum or bronchoalveolar lavage (BAL), recovery of *Aspergillus* species in BAL culture, positive polymerase chain reaction (PCR) for *Aspergillus* species in BAL or blood, or chest imaging consistent with a fungal infection.[4,5,7,12] However, these definitions underestimate disease burden in centers that do not routinely perform bronchoscopy. Some centers, especially those in North America, use lower limits to define positivity of biomarkers and employ screening with multiple antigen tests, including those that detect (1,3)- $\beta$ -D-glucan (BDG). Given diagnostic variability and clinical use of empirical antifungal therapy, a pragmatic approach to understanding the impact of CAPA warrants inclusion of multiple criteria to define disease. In this study, we aimed to describe risk factors, clinical course, and outcomes of adult patients with CAPA by applying proposed and expanded CAPA definitions in a large cohort of people with severe COVID-19 in the Johns Hopkins Medicine (JHM) Health System.[13]

## Methods

### Study Design and Data Source

This is a retrospective study that utilized the COVID-19 Precision Medicine Analytics Platform (PMAP) Registry (JH-CROWN), which includes data from all COVID-19 patients cared for at five hospitals in JHM. The registry includes patients who were admitted and diagnosed with COVID-19 by a positive SARS-CoV-2 nucleic acid amplification test (NAAT). Patient-level information such as demographics, medical history, laboratory tests, inpatient therapy including specific time points of each intervention, and discharge disposition were available for analyses. This study was approved by the Institutional Review Board at Johns Hopkins University.

### Study Population

This study included mechanically ventilated COVID-19 adult patients whose admission date was between March and August 2020. Patients who were intubated before admission or hospital transfer were analyzed as having been intubated since admission. Patients who were extubated prior to admission (such as in the emergency department) were excluded. All patients were followed from the time of admission until death, or discharge, with the last patient being discharged on October 19, 2020.

Starting in April 2020, institutional recommendations were to screen mechanically ventilated patients in ICUs for fungal infections by serum *Aspergillus* GM enzyme immunoassay (GM EIA) (Platelia™, BIO-RAD), serum BDG (Fungitell®, Associates of Cape Cod, Inc.), and fungal cultures from respiratory samples. Radiography included chest X-rays and computed tomography (CT), if deemed feasible. Antimicrobials, including antifungal therapies were administered by clinical teams when a fungal infection was considered to be associated with clinical deterioration, and when laboratory and radiographic findings compelled consideration

of secondary complications of COVID-19. Bronchoscopy was performed when considered feasible.

### CAPA Case Definitions

“Probable CAPA” was defined as having one of the following conditions: presence of new cavitory lung lesion(s) on chest CT without alternative explanation, positive serum GM EIA index  $\geq 0.5$ , positive BAL GM index  $\geq 1.0$ , or positive culture for *Aspergillus* species in BAL.[4,5,7] As our institution relies on FDA-cleared cut-offs for positive BAL GM at index  $\geq 0.5$ , uses additional markers (BDG) to screen for fungal infections, and performs screening cultures with other respiratory fluids, we included a pragmatic definition of “possible CAPA.” This included at least one of the following conditions: positive BAL GM index 0.5 – 1.0; positive serum BDG  $\geq 80$  pg/ml without alternative explanation; or culture with growth of *Aspergillus* species in non-BAL respiratory samples, namely endotracheal aspirates. Individual case ascertainment was confirmed through rigorous chart review. The time of CAPA diagnosis was defined as the earliest date on which diagnostic feature was identified. The main analysis used the expanded CAPA definitions which included probable and possible CAPA (herein simply called CAPA). Additional subgroup analyses were performed to compare differences between the more conservative definition (probable CAPA) to those without infection. Sensitivity analyses were performed to compare the outcomes between people who were diagnosed with CAPA by only positive serum BDG vs other CAPA criteria.

### Statistical Analysis

All analyses were performed using Stata 15.1/SE (College Station, TX). Patient comorbidities were derived from the defined International Classification of Diseases (ICD)-10 code components of Elixhauser Comorbidity Index (Supplementary Table 1) in conjunction with chart review.[14] Analyses of patient demographics and baseline characteristics among different groups were conducted by Wilcoxon rank-sum test and Fischer’s exact test

depending on types of variables. An  $\alpha$  of 0.05 was used to determine statistical significance. All confidence intervals were 95% and reported as per the method of Louis and Zeger.[15]

Using the time stamps of events available in the JH-CROWN and patient charts, we evaluated longitudinal COVID-19 severity throughout admission. The WHO COVID-19 ordinal severity score ranges from 1 (ambulatory, no limitations) to 8 (death) and has previously been used as a metric of COVID-19 severity.[16,17] COVID-19 severity scores at admission and peak severity scores during admission were compared among different CAPA definitions by using Wilcoxon rank-sum test. The trajectory of severity scores throughout admission among different groups were analyzed by using multilevel mixed-effects ordinal logistic regression, adjusting for severity within 24-hours of admission, including a patient-level random intercept and an interaction between CAPA diagnosis and time since admission. The odds ratio of this interaction represented the difference in the “slope” of severity plotted against time; statistical significance indicates that one group has faster disease progression (increasing severity,  $OR > 1$ ) or recovery (decreasing severity,  $OR < 1$ ) over time during admission. Since a patient's severity score could change several times in a day, the duration of time at a given severity score was calculated in minutes and later converted to days. The maximum score from each “day” represented patient's severity in each 24-hour time frame and was used to graph and analyze the trajectory of disease severity.

Vasopressors (IVP), extracorporeal membrane oxygenation (ECMO), and continuous renal replacement therapy (CRRT) were included in advanced life support therapy. We used Fine and Gray competing risks regression to obtain a subhazard ratio (sHR) of outcomes, similar to a hazard ratio used in Cox regression but accounting for competing events.[18] In analyses of mortality and hospital discharge, death was considered a competing event. Similarly, death was considered a competing event in analyses of receipt of advanced life support therapy, and extubation. Times from intubation to an event were converted from

minutes to days, allowing for non-integer follow-up durations. As IVP could be administered prior to intubation, patients who received IVP prior to intubation were given a minute's duration of follow-up time to reflect the progression of severity in the entire cohort.

## Results

### Patients Demographics and Baseline Characteristics

A total of 396 patients were included in this cohort: 20 probable CAPA, 19 possible CAPA, and 357 patients without CAPA. Demographics and baseline characteristics of the cohort (39 CAPA and 357 non-CAPA) are shown in Table 1. Compared to people without CAPA (controls), people with CAPA had significantly lower median BMI (26.6 vs 29.9,  $p=0.04$ ), but more underlying pulmonary vascular disorders, which included pulmonary hypertension and chronic pulmonary emboli (41% vs 21.6%,  $p=0.010$ ), liver disease (35.9% vs 18.2%,  $p=0.018$ ), coagulopathy (51.3% vs 33.1%,  $p=0.033$ ), solid tumors (25.6% vs 10.9%,  $p=0.017$ ), and multiple myeloma (5.1% vs 0.3%,  $p=0.027$ ) (Table1). People with CAPA had similar median age (IQR) (66 (55, 70) vs 63 (53, 72),  $p=0.8$ ) and female sex (43.6% vs 40.1%,  $p=0.7$ ), compared to non-CAPA, respectively. Median (IQR) duration from COVID-19 diagnosis to CAPA diagnosis was 15 (9, 23) days, and median (IQR) duration from intubation to CAPA diagnosis was 12 (3, 22) days. Similar baseline characteristics were seen in the more limited group of patients who met criteria for only probable CAPA (Supplementary Table 2).

Diagnostic characteristics incorporated within the two different definitions of CAPA were compared (Supplementary Table 3). Among 20 probable CAPA patients, 9 (45%) had cavitary lung lesions, 8 (40%) had positive serum GM EIA index  $\geq 0.5$ , 2 (10%) had positive BAL GM EIA index  $\geq 1$ , and 2 (10%) had positive culture for *Aspergillus* species in BAL. Among 19 patients with possible CAPA, 1 (5%) had positive BAL GM EIA index  $\geq 0.5$  (but less than 1.0), 9 (47%) had cultures revealing *Aspergillus* species from non-BAL respiratory samples, and 11 (60%) had positive BDG  $\geq 80$  pg/ml without alternative explanation

(Supplementary Table 3). Probable CAPA was diagnosed later than possible CAPA relative to COVID-19 diagnosis; median (IQR) duration from COVID-19 diagnosis to probable and possible CAPA diagnosis were 19 (11, 37) and 10 (4, 15) days, respectively ( $p = 0.006$ ); median (IQR) duration from intubation to probable and possible CAPA diagnosis were 13 (8.5, 28) and 8 (1, 13) days, respectively ( $p = 0.029$ ). Eleven of 20 (55%) probable CAPA and 8 of 19 (42.1%) of possible CAPA received mold active antifungal agents.

### Therapeutic Course and Outcomes

Compared to controls, patients with CAPA were more likely to have received corticosteroids during the index admission, particularly after intubation (53.8% vs 28.6%,  $p = 0.005$ , Table 2). Among different types of corticosteroid use during admission, there was only a statistically significant difference in hydrocortisone use in patients with CAPA compared to controls (38.5% vs. 12%,  $p < 0.001$ ). There was no significant difference in dexamethasone use in patients with CAPA vs their controls (23.1% vs 21%,  $p = 0.8$ , respectively). No differences in use of tacrolimus, mycophenolate mofetil, tocilizumab, remdesivir, and hydroxychloroquine was observed in patients with CAPA, compared to controls (Table 2). The same differences were evident when using the probable definition CAPA only (Supplementary Table 4).

People with CAPA had similar disease severity scores at admission compared to controls. However, the CAPA group had a higher maximum severity score during admission compared to controls, with median (IQR) score of 8 (7,8) vs 7 (7,8), ranksum  $p = 0.021$ , respectively (Table 3, Supplementary Figure 1). While both people with CAPA and controls deteriorated by increase in the severity scales, those with CAPA required significantly longer duration of any oxygen therapy [median (IQR) 40.7 (20, 69.9) vs 16.7 (10, 29.4) days,  $p < 0.001$ ], ventilator support [median (IQR) 36.6 (14.6, 63) vs 8.9 (3.8, 18.0) days,  $p < 0.001$ ], IVP [median (IQR) 24.8 (12.3, 46) vs 6.2 (1.7, 14.2) days,  $p < 0.001$ ], ECMO therapy [median (IQR) 55.4 (33.2, 68.5) vs 14.9 (11.4, 27.0) days,  $p = 0.024$ ], and hospital length of stay



[median (IQR) 41.1 (20.5, 72.4) vs 18.5 (10.7, 31.8),  $p < 0.001$ ] compared to controls (Table 3). Differences in severity of illness can be appreciated in the longitudinal depiction of mean daily ordinal score (Figure 1). CAPA patients had significantly slower recovery compared to controls (adjusted odds ratio (aOR)  $1.08$   $1.09$   $1.1$ ,  $p < 0.001$ ).

There were no differences in mortality between people with CAPA and controls (sHR  $0.9$   $1.3$   $1.9$ ,  $p = 0.2$ , Figure 2). Using subhazard functions for competing risk estimations, people with CAPA were extubated 2-times slower compared to those without (sHR  $0.4$   $0.5$   $0.6$ ,  $p < 0.001$ , Figure 2). Similarly, progression from severity score 6 (intubation) to 7 (receipt of other advanced life support) was 1.8-times faster among people with CAPA (sHR  $1.3$   $1.8$   $2.5$ ,  $p < 0.001$ , Figure 2). There was no difference in overall survival. However, people with CAPA had a longer inpatient stay and discharge rate was slower, compared to controls (sHR  $0.4$   $0.5$   $0.8$ ,  $p = 0.006$ , Figure 2).

Findings were largely the same when CAPA was analyzed using the probable definition only (Supplementary Table 5, Supplementary Figure 2). Like the larger group, people with probable CAPA also had longer durations of mechanical ventilation, hemodynamic support, and dynamics of severity scores following intubation (Supplementary Table 5 and Supplementary Figure 3). People with probable CAPA had no difference in mortality compared to those without but took longer to be extubated. Rate to extubation and progression in severity scores showed similar differences (Supplemental Figure 4). In this analysis with a smaller case sample size, there was only a trend towards differences in hospital length of stay between people with probable CAPA and controls (sHR  $0.4$   $0.6$   $1.0$ ,  $p = 0.08$ , Supplementary Figure 4). Sensitivity analyses did not reveal differences in clinical outcomes among people with CAPA by positive serum BDG alone and people with CAPA by other criteria (Supplementary Table 6).

## Discussion

We describe outcomes associated with CAPA amongst a large cohort of mechanically ventilated patients from 5 hospitals in the JHM Health System. Depending on definitions applied, the incidence of recognized CAPA ranged from 5 to 10%. People with CAPA had different underlying diseases, especially with regards to BMI, pulmonary, liver, and oncologic diseases prior to COVID-19, compared with those who did not develop CAPA. Regardless of definitions used, people with CAPA had uniformly worse outcomes compared to those without, especially with regards to severity of illness, ventilatory and hemodynamic support, and duration of hospitalization.

Aspergillosis as a complication of severe viral infection has been best documented in people with influenza.[19–23] Several large cohort studies have showed that rates of pulmonary aspergillosis in influenza patients requiring ICU admission range from 7-30%, depending on methods applied to diagnostic screening, seasonal viral epidemiology, and definitions applied to report “influenza associated aspergillosis”. [19–23] Early in the COVID-19 pandemic, European centers reported similarly high rates of pulmonary aspergillosis associated with COVID-19; rates have similarly varied depending on diagnostic methods and definitions.[4–10] It has been suggested that risks for both airway and invasive aspergillosis in this setting occur due to viral-mediated damage in airway fungal clearance and concurrent suppression of secondary immunologic defenses.[21,24] Underlying defects in fungal clearance and pre-existing immunosuppression likely explain observed risks associated with pulmonary disorders, solid tumors, and multiple myeloma in this cohort. Receipt of corticosteroids, particularly hydrocortisone, during admission appeared to be associated with increased risks for CAPA. Since hydrocortisone is given to people with critical illness, it is difficult to determine whether this reflects actual incremental risk or serves as a marker for illness severity.

European investigators have proposed 'probable' CAPA definitions that substantially reflect clinical practices that include aggressive bronchoscopy, use of PCR-based assays, and application of antigen (*Platelia galactomannan*) assay cut-offs at higher index levels (positive BAL GM index  $\geq 1.0$ ) to define positivity compared to what is currently recommended by the FDA.[12] Similar to many hospitals in North America, we do not commonly perform bronchoscopy for CAPA diagnosis or use PCR tests for *Aspergillus* species.[25] With these diagnostic differences, we observed lower CAPA rates compared to European prospective studies.[4,7] Given the different diagnostic approaches to CAPA, we used *a priori* expanded CAPA definitions to include a more pragmatic 'possible' category reflective of diagnostic practices in our institutions. Growth of organism in endotracheal aspirate cultures, positive BDG assays, and low-positive BAL GM EIA (positive BAL GM index 0.5 – 1.0) informed the majority of diagnoses within the 'possible' category. The definition is less conservative and may include more people with false positive microbiologic evidence (especially with the BDG assay), but possible CAPA represents approximately half of those patients by our current diagnostic approach. Earlier recognition of probable vs. possible CAPA may suggest that this group contains more people with invasive aspergillosis; however, the groups did not differ when considering host characteristics and outcomes.

People with CAPA (regardless of definition applied) had similar severity of illness compared to controls, at admission. However, people with CAPA improved slower during hospitalization when compared to their counterpart control groups, having increased durations of mechanical and hemodynamic support. Although there was no difference in overall mortality, it is likely that this study lacked the power to detect small differences amongst mechanically ventilated patients with COVID-19. Here, rates of death in patients with CAPA were consistent with those reported by other centers.[4,7] Whether CAPA caused these differences in outcomes or occurred because of other variables that dictate severe COVID-19 is unclear. It is notable that the underlying risks for CAPA do not mimic those that are typically associated with severe COVID-19. People with CAPA had lower BMIs

compared to controls, and no differences in age, hypertension, and gender, all risks classically associated with severe COVID-19.[1,26–29] While we did not compare outcomes of CAPA according to receipt of antifungal therapy because of the clinical bias inherent in retrospective design, results of prospective studies have suggested that antifungal therapy can improve outcomes.[4,7]. Approximately 50% of people with probable and possible CAPA received mold active antifungal agents. We suspect that the low rate of treatment was likely from lack of recognition in this emerging condition and difficulty in differentiation between invasive mold disease and colonization without standardized definitions, particularly in early COVID-19 pandemic.

Our study has several strengths: 1) the cohort included people with much heterogeneity in comorbidities, facilitating understandings of CAPA risks; 2) the study provided substantial CAPA cases as well as robust controls; 3) data were confirmed by rigorous review of patient-level records; 4) longitudinal analyses were performed to understand the clinical course trajectory of CAPA patients and their controls; and 5) attention was focused on diagnostic definitions, including ones that best reflect clinical practice in the institution. Limitations include those inherent to retrospective studies, including the potential of unknown confounders affecting clinical outcomes, use of ICD-10 data for patient comorbidities, and variability in clinical practice in ordering fungal biomarkers.

In conclusion, this large cohort study verified small, but substantial risks for CAPA in mechanically ventilated people in a large health system in the U.S. While differences in reported rates may reflect diagnostic heterogeneity, differences in patient comorbidities and therapeutic approaches, our findings mimic and expand upon those reported in smaller studies, in that CAPA is associated with poor outcomes, and risks reflect numerous underlying conditions that may predict poor airway clearance of fungus, combined with deficits in secondary antifungal defenses. Given difficulties in invasive sampling, improved non-invasive diagnostics that enable screening, and/or prophylactic antifungal therapy may be warranted in high-risk patients to improve COVID-19 outcomes.

## NOTES

### Contributors

N. Permpalung: study design, data collection, data analysis, manuscript writing, critical review; T. Chiang: study design, data collection, data analysis, manuscript writing, critical review; A. Massie: study design, data analysis, manuscript writing, critical review; S.X. Zhang: study design, manuscript writing, critical review; R. Avery: study design, manuscript writing, critical review; S. Nematollahi: manuscript writing, critical review; D. Ostrander: manuscript writing, critical review; D. Segev: manuscript writing, critical review; K.A. Marr: study design, data analysis, manuscript writing, critical review

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**Table 1. Demographics and baseline characteristics, comparing CAPA to non-CAPA**

	<b>Non-CAPA (N=357)</b>	<b>CAPA (N=39)</b>	<b>P-value</b>
Age, median (IQR)	63 (53, 72)	66 (55, 70)	0.8
Female sex	143 (40.1%)	17 (43.6%)	0.7
Race/ethnicity			0.9
White	88 (24.6%)	8 (20.5%)	
Black	140 (39.2%)	15 (38.5%)	
Hispanic	89 (24.9%)	12 (30.8%)	
Asian and others	38 (10.6%)	4 (10.3%)	
Unknown	2 (0.6%)	0 (0.0%)	
<b>BMI, median (IQR)</b>	<b>29.9 (25.6, 35.4)</b> <b>(n=268)</b>	<b>26.6 (24.5, 28.7)</b> <b>(n=25)</b>	<b>0.037</b>
Smoking status			0.9
Never smoked	169 (47.3%)	19 (48.7%)	
Ever smoked	125 (35.0%)	15 (38.5%)	
Unknown	63 (17.6%)	5 (12.8%)	
Diabetes mellitus, uncomplicated	182 (51.0%)	15 (38.5%)	0.18
Diabetes mellitus, complicated	178 (49.9%)	15 (38.5%)	0.18
Hypertension	265 (74.2%)	29 (74.4%)	1.0
Hypertension, complicated	163 (45.7%)	22 (56.4%)	0.24
Chronic pulmonary disease	112 (31.4%)	16 (41.0%)	0.28
<b>Pulmonary vascular diseases</b>	<b>77 (21.6%)</b>	<b>16 (41.0%)</b>	<b>0.010</b>
Congestive heart failure	125 (35.0%)	18 (46.2%)	0.22
Obesity	188 (52.7%)	16 (41.0%)	0.18
Peripheral vascular disorders	62 (17.4%)	6 (15.4%)	1.0
Renal failure	115 (32.2%)	17 (43.6%)	0.16
Fluid and electrolyte disorders	337 (94.4%)	38 (97.4%)	0.7
<b>Liver disease</b>	<b>65 (18.2%)</b>	<b>14 (35.9%)</b>	<b>0.018</b>
Hypothyroidism	54 (15.1%)	4 (10.3%)	0.6

Peptic ulcer disease excluding bleeding	11 (3.1%)	3 (7.7%)	0.15
Anemia, nutritional deficiency	220 (61.6%)	28 (71.8%)	0.23
Anemia, blood loss	16 (4.5%)	4 (10.3%)	0.12
<b>Coagulopathy</b>	<b>118 (33.1%)</b>	<b>20 (51.3%)</b>	<b>0.033</b>
Psychosis	42 (11.8%)	5 (12.8%)	0.8
Depression	101 (28.3%)	12 (30.8%)	0.7
Alcohol abuse	26 (7.3%)	1 (2.6%)	0.50
Drug abuse	30 (8.4%)	3 (7.7%)	1.0
Other neurological disorders	170 (47.6%)	21 (53.8%)	0.50
Paralysis	41 (11.5%)	7 (17.9%)	0.30
Rheumatoid arthritis/collagen vascular diseases	25 (7.0%)	1 (2.6%)	0.50
Weight loss	79 (22.1%)	14 (35.9%)	0.072
HIV/AIDS	7 (2.0%)	1 (2.6%)	0.57
<b>Solid tumor (with or without metastasis)</b>	<b>39 (10.9%)</b>	<b>10 (25.6%)</b>	<b>0.017</b>
Lymphoma	1 (0.3%)	1 (2.6%)	0.19
<b>Multiple myeloma</b>	<b>1 (0.3%)</b>	<b>2 (5.1%)</b>	<b>0.027</b>
Monoclonal gammopathy	9 (2.5%)	0 (0.0%)	0.6
Solid organ transplant	4 (1.1%)	0 (0.0%)	1.0

AIDS: adult immunodeficiency syndrome; BMI: body mass index; CAPA: COVID-19 associated pulmonary aspergillosis; HIV: human immunodeficiency virus; IQR: interquartile range; N: number.

**Table 2. Immunosuppressive agents and COVID-19 specific therapy, comparing CAPA to non-CAPA**

	Non-CAPA (N=357)	CAPA (N=39)	p-value
<b>Corticosteroids use during admission</b>			<b>0.005</b>
Pre-intubation	50 (14.0%)	5 (12.8%)	
Post-intubation	102 (28.6%)	21 (53.8%)	
No corticosteroids use	205 (57.4%)	13 (33.3%)	
<b>Prednisone during admission</b>	34 (9.5%)	2 (5.1%)	0.56
Median total dose, mg (IQR)	120 (60, 270)	160 (120, 200)	0.7
Median duration, days (IQR)	6 (2, 23)	2 (2, 2)	0.27
<b>Methylprednisolone during admission</b>	62 (17.4%)	10 (25.6%)	0.20
Median total dose, mg (IQR)	160 (60, 420)	245 (60, 400)	0.8
Median duration, days (IQR)	3 (1, 5)	3 (1, 7)	0.8
<b>Hydrocortisone during admission</b>	<b>43 (12.0%)</b>	<b>15 (38.5%)</b>	<b>&lt;0.001</b>
Median total dose, mg (IQR)	500 (150, 1000)	425 (300, 900)	0.9
Median duration, days (IQR)	4 (1, 8)	4 (3, 9)	0.7
<b>Dexamethasone during admission</b>	75 (21.0%)	9 (23.1%)	0.8
Median total dose, mg (IQR)	50 (20, 60)	36 (20, 60)	0.8
Median duration, days (IQR)	5 (2, 10)	6 (1, 10)	1.0
<b>Tacrolimus during admission</b>	4 (1.1%)	0 (0.0%)	1.0
<b>Mycophenolate mofetil during admission</b>	1 (0.3%)	0 (0.0%)	1.0
<b>COVID-19 specific therapy</b>			
Tocilizumab	63 (17.6%)	9 (23.1%)	0.39
Remdesivir	83 (23.2%)	9 (23.1%)	1.0
Hydroxychloroquine	104 (29.1%)	9 (23.1%)	0.58

CAPA: COVID-19 associated pulmonary aspergillosis; IQR: interquartile range; N: number

**Table 3. WHO COVID-19 severity scores, advance life support therapy, and clinical outcomes, comparing CAPA to non-CAPA**

	Non-CAPA (N=357)	CAPA (N=39)	p- value
WHO severity scores on day of admission, median (IQR)	5 (4, 6)	5 (4, 6)	0.55
<b>Maximum WHO severity scores during admission</b>			<b>0.03</b>
<b>Intubation</b>	<b>33 (9.2%)</b>	<b>0 (0.0%)</b>	<b>8</b>
<b>Intubation with advance life support therapy</b>	<b>180 (50.4%)</b>	<b>17 (43.6%)</b>	
<b>Death</b>	<b>144 (40.3%)</b>	<b>22 (56.4%)</b>	
<b>Maximum WHO ordinal scale during admission, median (IQR)</b>	<b>7 (7, 8)</b>	<b>8 (7, 8)</b>	<b>0.02</b>
Highest oxygen requirement on day 1 admission			0.11
Did not need oxygen on admission	34 (9.5%)	5 (12.8%)	
Need oxygen, but not HFNC or NIPPV	136 (38.1%)	9 (23.1%)	
HFNC or NIPPV	56 (15.7%)	11 (28.2%)	
Ventilator/intubation	131 (36.7%)	14 (35.9%)	
<b>Duration on oxygen therapy, median days (IQR)</b>	<b>16.7 (10.0, 29.4)</b>	<b>40.7 (20.0, 69.6)</b>	<b>&lt;0.001</b>
Any HFNC therapy during admission	217 (60.8%)	27 (69.2%)	0.39
Duration on HFNC, median days (IQR)	4.1 (0.9, 11.3) (n=217)	3.7 (2.0, 15.5) (n=27)	0.32
<b>Duration on ventilator, median days (IQR)</b>	<b>8.9 (3.8, 18.0)</b>	<b>36.6 (14.6, 63.0)</b>	<b>&lt;0.001</b>
<b>Any CRRT during admission</b>	<b>59 (16.5%)</b>	<b>15 (38.5%)</b>	<b>0.002</b>
Duration on CRRT, median days (IQR)	6.7 (2.6, 14.2) (n=59)	12.0 (3.1, 22.6) (n=15)	0.12
Any ECMO treatment	13 (3.6%)	4 (10.3%)	0.075
<b>Duration on ECMO, median days (IQR)</b>	<b>14.9 (11.4, 27.0)</b> <b>(n=13)</b>	<b>55.4 (33.2, 68.5)</b> <b>(n=4)</b>	<b>0.024</b>
Any inpatient hemodialysis	35 (9.8%)	8 (20.5%)	0.055

Duration on inpatient hemodialysis, median days (IQR)	13.7 (4.9, 31.5) (n=35)	31.4 (12.4, 55.1) (n=8)	0.22
<b>Any vasopressor treatment</b>	<b>297 (83.2%)</b>	<b>38 (97.4%)</b>	<b>0.01</b> <b>7</b>
Duration on vasopressor therapy, median days (IQR)	6.2 (1.7, 14.2) (n=297)	24.8 (12.3, 46.0) (n=38)	<0.0 01
Death at discharge	144 (40.3%)	22 (56.4%)	0.06 1
DNR/DNI at admission	27 (7.6%)	1 (2.6%)	0.34
<b>DNR/DNI during entire admission</b>	<b>155 (43.4%)</b>	<b>24 (61.5%)</b>	<b>0.04</b> <b>1</b>
Hospital length of stay (admission to discharge), median days (IQR)	18.5 (10.7, 31.8)	41.1 (20.5, 72.4)	<0.0 01
Time since intubation to discharge, median days (IQR)	15.9 (8.3, 29.2)	39.8 (19.7, 66.1)	<0.0 01

CAPA: COVID-19 associated pulmonary aspergillosis; CRRT: continuous renal replacement therapy; DNI: do not intubate; DNR: do not resuscitate; ECMO: extracorporeal membrane oxygenation; HFNC: high flow nasal cannula; IQR: interquartile range; N: number; NIPPV: noninvasive positive-pressure ventilation; WHO: World Health Organization

## Figure Legends

Figure 1. Trajectory of Mean Daily Maximum WHO Severity Score between CAPA and non-CAPA patients (1A time since admission; 1B time since intubation)

Figure 2 Cumulative incidence of in-patient mortality (2A), extubation (2B), advanced life support therapy (2C), and hospital discharge (2D) after intubation

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Figure 1

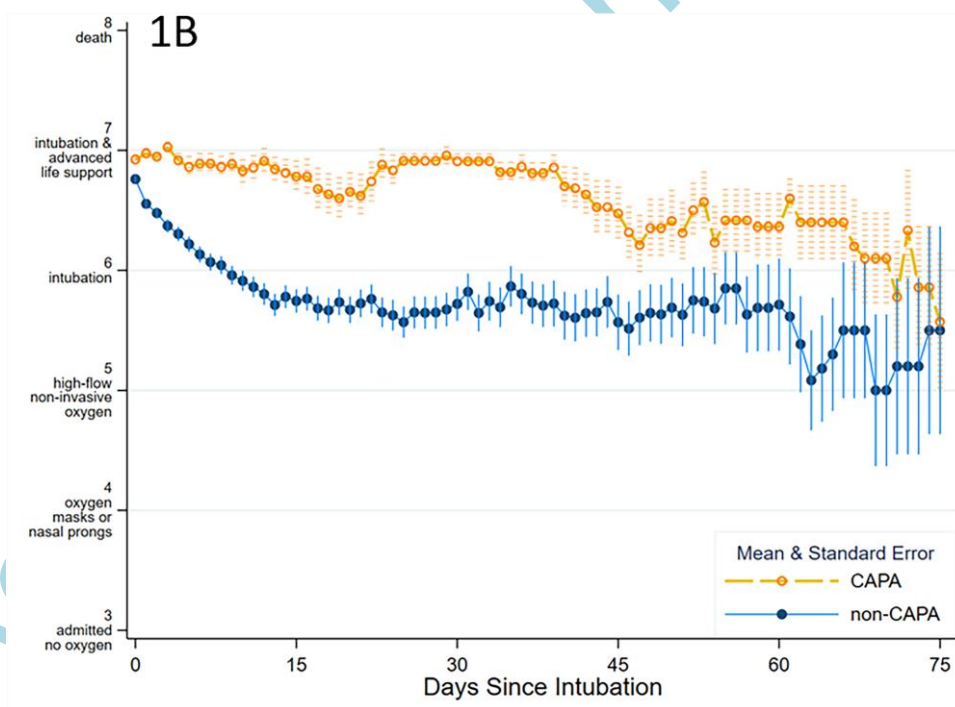
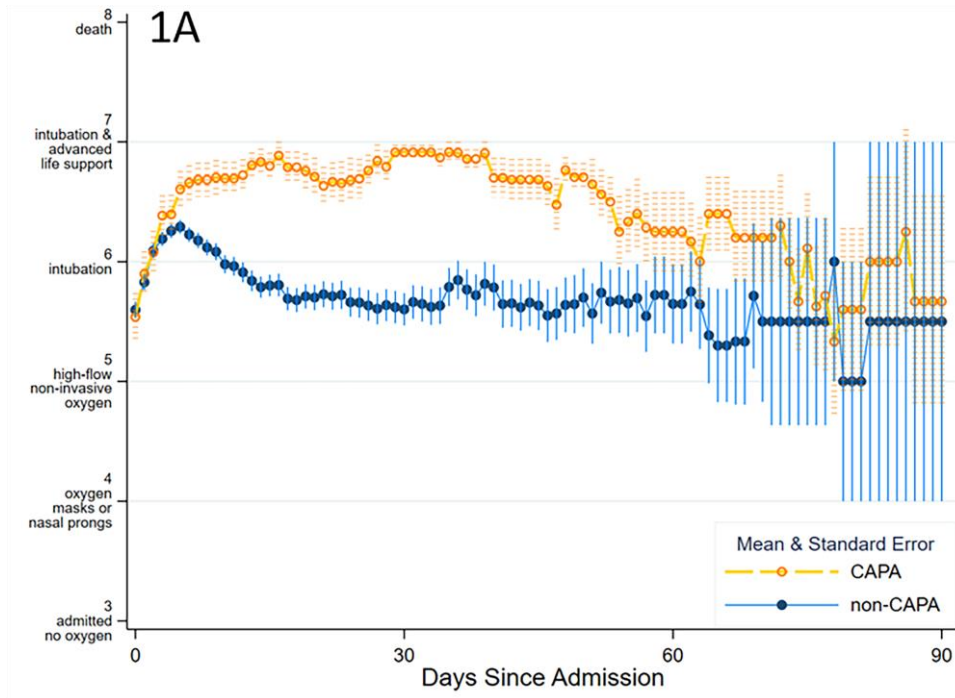


Figure 2

