International Journal of Community Medicine and Public Health
*Chatterji S et al. Int J Community Med Public Health. 2023 Jul;10(7):2506-2513*
http://www.ijcmph.com
pISSN 2394-6032 | eISSN 2394-6040

DOI: https://dx.doi.org/10.18203/2394-6040.ijcmph20232045

**Original Research Article**

# A retrospective observational study on incidence and clinico-epidemiological features of COVID-19 associated pulmonary aspergillosis among cancer patients hospitalized with COVID-19 in a tertiary care cancer centre of India

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**Received:** 05 March 2023
**Accepted:** 16 June 2023

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## ABSTRACT

**Background:** COVID-19 associated pulmonary aspergillosis (CAPA) is an emerging complication among patients with COVID-19 but hasn't been well studied in cancer patients. This study, we try to find out important aspects associated with CAPA among cancer patients with regards to clinico-epidemiological factors.
**Methods:** In this retrospective observational study, we included 198 consecutive patients COVID-19 between April 2020 and February 2021. CAPA cases were classified according to CAPA-European Confederation of Medical Mycology criteria (2020 ECMM/ISHAM consensus criteria).
**Results:** The overall incidence of CAPA was found to be 10.1% in our study population. The incidence among hematological malignancies was 11.25% and solid tumors was 10%. In-hospital mortality was significantly high among patients with CAPA as compared to that among without CAPA (40% versus 16.85%; p<0.012695). Significant number of patients with CAPA had received chemotherapy in last 3 months before diagnosis of COVID-19 (50% versus 28.09%, p=0.043222) and had evidence of culture positive bacterial infection (30% versus 5.62; p=0.000888). Significantly more patients having CAPA were on steroids, required oxygen and/or ventilator support as compared to those without CAPA.
**Conclusions:** CAPA is a significant cause of mortality and length of hospital stay (16 versus 7 days; p=0.00001) among cancer patients with COVID-19. Cancer patients with COVID-19 were at increased risk of CAPA as compared to non-cancer patients.

**Keywords:** Cancer, invasive aspergillosis, CAPA, COVID-19

## INTRODUCTION

Coronavirus disease-19 (COVID-19)-associated pulmonary aspergillosis (CAPA) has emerged as an important invasive opportunistic infection during the pandemic. It is known to affect previously immunocompetent or immuno-compromised, mainly mechanically ventilated and intensive care unit (ICU) patients.[1] A systematic review and meta-analysis reported incidence and mortality of CAPA in the ICU to be 10.2% (95% CI, 8.0-12.5; $I^2$=82.0%) and 54.9% (95% CI, 45.6-64.2; $I^2$=62.7%) respectively. As in influenza associated

pulmonary aspergillosis (IAPA), there are many unanswered questions regarding the diagnostic criteria used to define CAPA. Radiological findings of Coronavirus disease-19 (COVID-19) and invasive aspergillosis (IA) are nonspecific and show considerable overlap. Moreover, broncho-alveolar lavage (BAL) is often unavailable as the practice of bronchoscopy is restricted in COVID-19 due to infection control concerns.[2] Thus, calculating exact incidence of CAPA and comparison amongst various studies is difficult. Recently, European Confederation Of Medical Mycology and the International Society for Human and Animal Mycology (ECMM/ISHAM) consensus criteria for diagnosis of CAPA was published.[3]

Patients with CAPA may lack classic host factors for invasive fungal diseases. It is thought that immune dysregulation associated with acute respiratory distress syndrome (ARDS), disrupted ciliary clearance and lymphopenia due to respiratory viral infection may all contribute to the development of CAPA.[4] Furthermore, treatment with tocilizumab and dexamethasone, usage of broad-spectrum antibiotics were also hypothesized to increase the risk of IA in COVID-19.[5]

Literature on CAPA amongst cancer patients with COVID-19 is scarce especially from low- middle income countries. In a systematic review and meta-analysis from USA, there was no significant effect of cancer on incidence of CAPA though CAPA patients were older and underlying chronic obstructive pulmonary disease (COPD) was common in this report.[6] Iqbal et al found underlying malignancy and cirrhosis to be significant risk factors for CAPA.[7] Another review mentions COPD, CKD (chronic kidney disease), heart disease, history of corticosteroid use and obesity as risk factors for CAPA.[8] Though initial case reports do not describe antibiotic usage much, broad spectrum antibiotic use is thought to predispose to CAPA.[9,10] In the study by Rothe et al among 50 patients admitted to the intensive care unit, Enterobacterales (34.0%) and *Aspergillus fumigatus* (18.0%) co-infections were found.[11] Other reports also highlighted a few bacterial co-infections with CAPA.[12-14]

Two studies have indicated that CAPA patients have excess mortality of 16% and 25% as compared with patients without evidence for aspergillosis. These excess mortality rates are similar to that found for patients with IAPA (influenza associated pulmonary aspergillosis), in whom the survival rate in intensive care units (ICUs) was 24% lower than in patients without this secondary infection.[3] Various other studies also found relation between diagnosis of CAPA and increased mortality but none found CAPA to cause significant increase in length of ICU stay.[6,7,15]

Radiological diagnosis of CAPA is difficult as thoracic CT scans may be non-specific in patients with COVID-19 usually showing ground-glass opacities, a crazy-paving pattern and patchy consolidations.[16] A lower proportion of well-circumscribed nodules, tree-in bud, and bronchial wall thickening (which are more specific for invasive aspergillosis) was observed for CAPA than IAPA patients in a retrospective study published from France[17]. Classic findings of angioinvasive fungal infection (infarct shaped consolidation, cavity, halo signs, mass or nodules were seen only rarely in another study on CAPA.[18]

As data was scarce on incidence and clinico-epidemiological characteristics of CAPA among cancer patients with COVID-19 and as various studies have shown increased morbidity and mortality in CAPA patients we decided to undertake this study.

## METHODS

### *Study design and participants*

This retrospective observational study was conducted at a tertiary cancer center of Kolkata, India. April 2020 to February 2021, a total of 224 patients admitted with COVID-19 were retrospectively included in this study.

Patients already diagnosed to have invasive Aspergillosis prior to the diagnosis of COVID-19 were excluded.

The study was approved by the institutional review board of Tata Medical Center, Kolkata (reference number ECWV/20/TMC/52/20 16.09.2020).

### *CAPA definitions*

In this study we have followed CAPA-European Confederation of Medical Mycology criteria (2020 ECMM/ISHAM consensus criteria).[3]

### *COVID case definitions*

Case definitions of mild, moderate and severe COVID were as per "clinical management protocol: COVID-19 version 3 13/06/2020. Government of India. Ministry of Health and Family Welfare.[19]

### *Sample collection, storage*

Samples of nose swab and throat swab (HiMedia Laboratories, Mumbai, India) were collected in VTM (Viral Transport Medium) and stored at minus 80ºC till the time of processing.

### *Microbiological, Mycological and virological methods*

Galactomannan (GM) detection (Platelia Aspergilllus Ag, Bio-Rad Laboratories, Munich, Germany) was performed in serum samples and in BAL samples gained by deep tracheal suction with a closed suction system from the lower respiratory tract.

For microbiological culture, approx. 5µl BAL fluid was plated on each agar plate. For each of the sample a blood and chocolate agar (prepared culture media, bioMérieux, France) were done separately and incubated in 5% $CO_2$ condition. A MacConkey agar (BD Difco, USA) used for differentiation purpose. All plates were incubated for 48 hrs at 37°C. A separate Sabouraud dextrose agar (BD Difco, USA) also done for fungal culture.

When growth of *Aspergillus spp*. could be established, it was then sub-cultured on sabouraud-dextrose-agar (BD Difco, USA) Aspergillus sub-cultures on sabouraud-dextrose-agar were incubated for 48-72 hours before species identification) for species identification via macroscopic, microscopic and ITS sequence-based analysis.

### *SARS-CoV-2 testing*

SARS-CoV-2 infection was detected by reverse-transcriptase-polymerase-chain-reaction (RT-PCR) assay done on nasopharyngeal sample in every patient by using TRUPCR kit (3B BlackBio Biotech, India). The time to RT-PCR negativity was calculated from the date of positivity to the date of first negative swab, with cases that had active COVID-19 infection at the time of analysis censored at the last follow-up. Data were extracted from the electronic medical records, excel datasheets maintained by the department, and hospital COVID-19 database, after approval from the institutional ethics committee.[20]

### *Aspergillus PCR*

The TaqMan based in-house real-time PCR assay was carried out with the custom designed 28S rRNA region specific primers and probes (Sigma-Aldrich, USA).[21] Specificity of the primers and probes were checked using NCBI blast (http://www.ncbi.nlm.nih.gov/tools/primer-blast). The following sequences of the forward primer 5'-TCTAAATGGGTGGTAAATTTC'3, reverse 5'-CATCTTTCGATCACTCTACT'3 and the probe were 6[FAM]GCTAAATACTGGCCGGAGACC[BHQ1] were used for the PCR assay. Each reaction contains 12.5 ulQuantitect multiplex PCR master mix (Qiagen, MA, USA), 250 mM of each primer (forward and reveres) with 150nM of probe (Reporter FAM, Quencher TAMRA) and 5 µl of DNA template were used. PCR reaction were run on the Rotor Gene Q (Qiagen, France) thermocyclers with a total reaction volume of 25µl with 40 cycles with a initial hold at 95°C for 10 minutes following cycling consisting of 95°C for 30 seconds, annealing at 55°C for 60 seconds, and finally acquiring through the green channel.

### *Statistical analysis.*

Continuous variables were shown as median and categorical variables as counts and percentages. For categorical variables statistical tests used are Chi-square test for equality of proportions and Fisher's exact test for count data. Statistical analysis done using statistical package R version 3.5.3 and MS Excel. P values <0.05 are considered as statistically significant.

## RESULTS

### *Patient demography*

One hundred ninety-eight patients were included in the study of which 119 were males. Males were predominant among patients with and without COVID-19 associated pulmonary aspergillosis (CAPA) (Table 1). Amongst our study population 40.4% (80 out of 198) patients had hematological malignancies (distribution shown in Figure 1 and 2) of whom 35.2% had non-Hodgkin lymphoma (NHL).

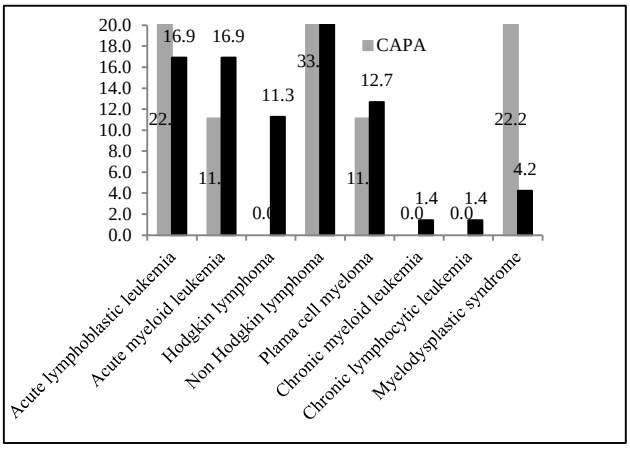


**Figure 1: Distribution of patients with haematological malignancies between CAPA and non-CAPA groups (with CAPA n=71, without CAPA n= 9).**

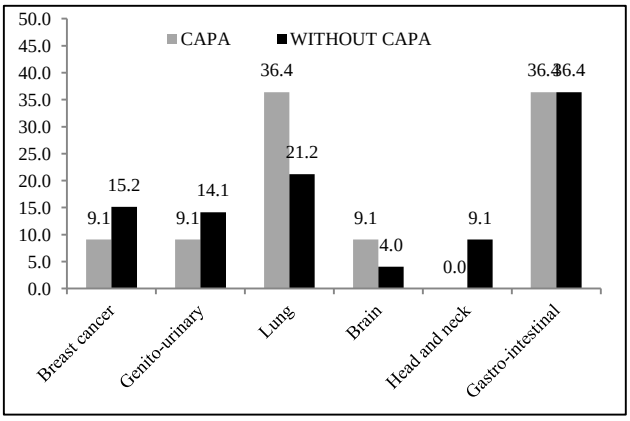


**Figure 2: Distribution of patients with solid malignancies between CAPA and non-CAPA groups (with CAPA n=11, without CAPA n= 99).**

Amongst the patients with solid organ malignancies (110 patients), 36.36% had gastro-intestinal cancers while 21.2% had lung cancer. 8 of our patients did not have confirmed diagnosis of malignancy during the admission.

One patient was post autologous stem cell transplant (for plasma cell myeloma) and he was diagnosed with CAPA and also died. The distribution of patients with various risk factors is depicted in Table 1. Fifteen percent and 24.16% of the patients with and without CAPA respectively were diabetic. The demographic data and the co-morbidities were comparable between the two groups (with CAPA and without CAPA).

**Table 1: Various risk factors, clinical features and outcome of patients with and without CAPA (COVID-19 associated pulmonary aspergillosis).**

| | With CAPA (n=20) | Without CAPA (n=178) | Odds ratio | P value | Statistical test done |
|---|---|---|---|---|---|
| **Baseline characteristics** | | | | | |
| Median age, years (range) | 59.5 (26-79) | 60 (4-87) | | | - |
| Male/Female sex ratio | 2.33 | 1.43 | | | - |
| **Risk factors n (%)** | | | | | |
| COPD/Asthma | 0 (0.00%) | 1 (0.56) | 0 | 1 | Fisher's exact test for count data |
| DM type 2 | 3 (15%) | 43 (24.16%) | 0.555 | 0.5761 | Fisher's exact test for count data |
| Hypertension | 8 (40.00%) | 66 (37.08%) | 1.13 | 0.9902 | Chi-square test for equality of proportions |
| Coronary heart disease | 0 (0.00%) | 5 (2.81%) | 0 | 1 | Fisher's exact test for count data |
| CKD | 0 (0.00%) | 3 (1.69%) | 0 | 1 | Fisher's exact test for count data |
| Nutropenia (1500/mm$^3$) | 1 (5.00%) | 12 (6.74%) | 0.729 | 1 | Fisher's exact test for count data |
| D-dimer (>1000) | 8 (40.00%) | 14 (7.87%) | 7.669 | 0.00035* | Fisher's exact test for count data |
| Average duration (in days) of steroid at diagnosis of CAPA | 5.55 (n=13) | 4.53 (n=26) | | | - |
| Average dose (in mg) of steroid (dexamethasone equivalent) at diagnosis of CAPA | 7.07 (n=13) | 7.2 (n=73) | | | - |
| **COVID-19 specific characteristics** | | | | | |
| Duration of symptoms before hospital admission, (in days) | 3 | 6 | | 0.017918 | Fisher's exact test for count data |
| Influenza PCR positive | 1 (2.17) | 3 (1.68) | | 0.312422 | Fisher's exact test for count data |
| **ICU data** | | | | | |
| Renal replacement (%) | 0 (0.00%) | 2 (1.12%) | 0 | 1 | Fisher's exact test for count data |
| **Outcome data** | | | | | |
| Median days of hospital stay in days (range) | 16 (4-48) | 7 (1-27) | | 0.00001 | Fisher's exact test for count data |
| In hospital mortality (%) | 8 (40%) | 30 (16.85%) | 3.263 | 0.03029* | Fisher's exact test for count data |
| Bacterial culture positive | 6 (30.00%) | 10 (5.62%) | 7.072 | 0.00208* | Fisher's exact test for count data |
| **Drug history** | | | | | |
| Steroid | 13 (65.00%) | 65 (36.52%) | 3.209 | 0.02572* | Chi-square test for equality of proportions |
| Broad spectrum antibiotics | 16 (80.00%) | 133 (74.72%) | 1.351 | 0.7866 | Fisher's exact test for count data |
| Chemotherapy in last 3 months before COVID-19 | 10 (50.00%) | 50 (28.09%) | 2.546 | 0.07757 | Chi-square test for equality of proportions |

* P value <0.05 (significant).

**Table 2: Distribution of types of oxygen support required between patients with and without CAPA (COVID-19 associated pulmonary aspergillosis).**

| Oxygen Requirement | Patients with CAPA (n= 20) | Patients without CAPA (n=178) | | P value |
|---|---|---|---|---|
| **Oxygen upto 15 litres/minute** | 9 (45.00%) | 10 (5.61%) | 13.372 | 8.36e-06* |
| **Mechanical ventilation** | 4 (20.00%) | 4 (2.25%) | 10.607 | 0.004153* |
| **Non-invasive ventilation** | 5 (25.00%) | 5 (2.81%) | 11.24 | 0.001158* |
| **High flow nasal oxygen** | 2 (10.00%) | 1 (0.56%) | 19.017 | 0.02744* |
| **Total patients requiring oxygen** | 20 (100%) | 20 (11.24%) | Inf | <2.2e-16* |

* P value <0.05 (significant).

***Incidence of CAPA***

The overall incidence of CAPA was found to be 10.1% (20 out of 198 patients). The incidence among patients with hematological malignancies was 11.25% (9/80) and that among patients with solid tumors was 10% (11/110). All patients had probable CAPA as per CAPA-European Confederation of Medical Mycology criteria (2020 ECMM/ISHAM consensus criteria).[3] Six (30%) patients had serum galactomannan value of ≥1.0, seven (35%) had serum galactomannan between 0.7 and 1.0 and the rest (35%) had the serum galactomannan index between 0.5 and 0.7. One patient underwent bronchoscopy and his broncholaveolar lavage (BAL) sample revealed hyaline septate hyphae.

***Clinical features and mortality***

Those patients who were diagnosed with CAPA presented significantly early for hospitalization (Table 1) and had increased length of stay as well (Table 1). While 65% of those with CAPA received steroid, only 36.52% of those without evidence of CAPA received corticosteroid (p=0.02572). But the average dose and duration of steroid used were similar in both the groups. In hospital mortality was significantly high among patients with CAPA as compared to those without CAPA (40% versus 16.85%; p<0.03029). Significantly more number of patients with CAPA had received chemotherapy in last 3 months before diagnosis of COVID-19 as compared to those without CAPA (50% versus 28.09%, p=0.043222). Of the patients with solid tumors who had CAPA 36.4% (4/11) had lung cancer and another 36.4% had gastro-intestinal tract malignancies, while 33.33% (3/9) patients with hematological malignancies with CAPA had non-Hodgkin's lymphoma (Figures 1 and 2). Patients with CAPA had significantly more evidence of culture positive bacterial infection than those without CAPA (30% versus 5.62; p=0.00208), but antibiotic usages noted among patients with and without evidence of CAPA were not significantly different (80% versus 74.72%; p=0.603838). Among patients in the study population who had negative bacterial cultures but were receiving antibiotics 30.83% patients had procalcitonin >0.05 ng/ml. Overall we found 8.08% bacterial co-infections amongst this cohort of COVID-19 patients with CAPA and 83.71% of our study population received broad spectrum antibiotics. The distribution of modalities of oxygen delivery used among the two groups is shown in (Table 2). Significantly more patients having CAPA required oxygen and or/ ventilator support as compared to those without CAPA. Significantly more patients with CAPA had D-Dimer more than 1000 ng/ml (40% versus 7.87%; p=0.00035).

***Radiological findings of patients with CAPA***

Among the CAPA patients ground glass opacities (GGOs) with/ without patchy consolidation and were most common radiological abnormalities observed in 45% of CAPA patients. Pleural effusion with or without consolidation was also noted. Around 5 patients had infiltrates on CXR that increased but could not be transported for (computed tomography) CT scan.

## DISCUSSION

As discussed previously, we could not find literature directly pertaining to CAPA amongst cancer patients with CoViD 19.[22] Incidence of CAPA (probable) in our cohort was similar to that found in the systematic review and meta-analysis by Mitaka et al but was definitely more than other reports which found incidence of CAPA to be 5% or lower.[4,23-25] The incidence was quite low as compared to earlier data which revealed an incidence well above 30%.[15,24] The lower incidence of CAPA found in recent studies may have been due to availability of standardized definition of CAPA by ISHAM/ECMM.[3] Our incidence, which was higher when compared to contemporary data, may have been influenced by underlying cancer and its treatment as incidence of CAPA was more among patients who underwent chemotherapy up to three months prior to be diagnosed with CAPA in our study. Mortality of our CAPA patients was significantly more than our patients without CAPA. These findings corroborate with published data which reported mortality in patients with CAPA.[4,15,26,27]

While other studies found COPD, CKD, steroid use, old age and pre-existing heart disease as risk factors for CAPA, we did not find any significant difference in prevalence of these risk factors amongst patients with and without CAPA, though dose and duration of steroid use for treatment of COVID-19 were found to be bit higher in

patients with CAPA than in those without the disease, these differences were not significant.[5-8] Interestingly we found significantly more patients in the CAPA arm received steroid as compared to the other arm. In our study we found significantly more culture positive bacterial co-infections among patients of COVID-19 with CAPA than among those without CAPA. But, interestingly, we did not find any significant difference in use of broad spectrum antibiotics among those with and without aspergillosis. Though most of the early papers did not look into co-infections, some reported bacterial co-infections in CAPA.[11-13] Still the literature on incidence of bacterial co-infections in patients with CAPA and the role of such co-infections remain scarce. A study from India recently reported that bacterial or fungal co-infection amongst COVID-19 patients was as low as 3.6%, while we found 8.08% bacterial super-infections/co-infections in our study population.[14] Despite this broad spectrum antibiotic was used very commonly in COVID-19 patients as reported in various studies.[28,29] Our findings probably reinforce this observation as we found 83.71% patients received broad spectrum antibiotics despite low incidence of culture positive bacterial infections. In concordance with various studies that found increased oxygen requirement and increased length of stay in patients with CAPA, we also observed the same in our study.[30-32] Also, we found that patients who were later diagnosed with CAPA presented significantly early to hospital as compared to those without CAPA. The cause of this was not clear. This highlights that CAPA increases morbidity and increases burden on already over-burdened healthcare system. We found D-dimer was more than 1000 ng/ml in significantly more patients with CAPA. D-Dimer is known to be a prognostic marker in CoViD-19 and elevated D-Dimer predicted in hospital mortality in a few studies.[33] Lung cancer patients were found to have high incidence of CAPA in our study. Structural lung disease and lung cancer have been mentioned as risk factors of CAPA in various publications.[34,35] We also found that incidence was CAPA was substantial amongst patients with cancers of gastro-intestinal tract and among patients with non-Hodgkin's lymphoma (NHL), but that may be due to more number of patients with these malignancies in our cohort. Moreover, NHL patients get steroids and also rituximab, both of which are known to increase risk for invasive fungal infections while patients with GI malignancies often have poor nutritional status.

Our study was probably the first on CAPA amongst cancer patients with COVID-19. In this study we analysed the various risk factors and outcomes of cancer patients with CAPA. We also looked into bacterial co-infections/super-infections amongst cancer patients with CAPA patients in particular and cancer patients with COVID-19 in general as data was lacking in these aspects too.

The limitations of our study were that it was a retrospective observational study and our study population was small. We also did not look into details of type of treatment that these patients were getting for cancer. Furthermore, we could not get CT scan done for all patients due to various logistic issues, though it is preferred imaging modality as per ECMM/ISHAM criteria.[3]

## CONCLUSION

Incidence of CAPA was observed to be higher in cancer patients with COVID-19 as compared to recently published literature on incidence of CAPA among non-cancer patients. CAPA increased mortality and length of hospital stay significantly among COVID-19 patients with cancer. Significantly more patients with CAPA had culture proved bacterial infection and received steroids as compared to patients without CAPA. The limitations of this study were that it was small and was retrospective in design. Further well designed studies on the subject are needed.

## ACKNOWLEDGEMENTS

We would like to thank Mr. Arup Seal, data entry operator at our hospital and Mr. Souvik Manna helped us with record keeping and data entry.

*Funding: No funding sources*
*Conflict of interest: None declared*
*Ethical approval: The study was approved by the Institutional Ethics Committee of Tata Medical Center, Kolkata (ref no. ECWV/20/TMC/52/20 16.09.2020)*

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**Cite this article as:** Chatterji S, Bhattacharya S, Mukherjee S, Bhattacharya PS, Goel G, Das P, et al. A retrospective observational study on incidence and clinico-epidemiological features of COVID-19 associated pulmonary aspergillosis among cancer patients hospitalized with COVID-19 in a tertiary care cancer centre of India. Int J Community Med Public Health 2023;10:2506-13.