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Comparison of risk factors and outcome of patients with and without COVID-19-associated pulmonary aspergillosis from Pakistan: A case–control study

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Abstract

Background: Early identification of COVID-19-associated pulmonary aspergillosis (CAPA) is particularly challenging in low- middle-income countries where diagnostic capabilities are limited, and risk factors for CAPA have not been identified. It is also essential to recognise CAPA patients who are likely to have a poorer outcome to decide on aggressive management approaches. Therefore, this study aimed to identify risk factors and outcomes for CAPA among admitted moderate to critical COVID-19 patients at our centre in Pakistan.

Methods: An unmatched case–control study with ratio of 1:2 was conducted on hospitalised adult patients with COVID-19 from March 2020–July 2021. Cases were defined according to European Confederation of Medical Mycology and the International Society for Human and Animal Mycology consensus criteria. Controls were defined as patients hospitalised with moderate, severe or critical COVID-19 without CAPA.

Results: A total of 100 CAPA cases (27 probable CAPA; 73 possible CAPA) were compared with 237 controls. Critical disease at presentation (aOR 5.04; 95% CI 2.18–11.63), age ≥ 60 years (aOR 2.00; 95% CI 1.20–3.35) and underlying co-morbid of chronic kidney disease (CKD) (aOR 3.78; 95% CI 1.57–9.08) were identified as risk factors for CAPA. Patients with CAPA had a significantly greater proportion of complications and longer length of hospital stay (p-value < .001). Mortality was higher in patients with CAPA (48%) as compared to those without CAPA (13.5%) [OR = 6.36(95% CI 3.6–11)].

Conclusions: CAPA was significantly associated with advanced age, CKD and critical illness at presentation, along with a greater frequency of complications and higher mortality.

KEYWORDS
COVID-19, COVID-19-associated pulmonary aspergillosis, mortality, risk factors

1 | INTRODUCTION

COVID-19-associated pulmonary aspergillosis (CAPA) is now a well-recognised complication in seriously ill patients with COVID-19 pneumonia. CAPA cases have been mainly reported from Europe with few studies from other regions. A recent multinational study from nine countries reported a variable prevalence of CAPA within various centres with a median prevalence ranging from 1.7% to 26.8%.[1] Another study reported 186 CAPA cases from 17 different countries between March 1 and August 31, 2020, inclusive of countries from low- and middle-income countries (LMICs).[2] Severe COVID-19 requiring intensive care unit (ICU) admission, mechanical ventilation and a high severity score on ICU admission has been consistently reported as a risk factor for CAPA.[3]

Although Pakistan was among the first countries to report CAPA as a complication in COVID-19 patients,[4] data from other LMICs have been limited. Previously, a case of proven CAPA was reported by Salehi M et al.[5] from Iran, but recently a systematic review of nine studies comprising data on COVID-19-associated fungal infections from Iran has reported 29 cases of Aspergillosis.[6] Early diagnosis and timely management of CAPA are critical due to its higher mortality and worse outcome. This is particularly challenging in LMICs where delays due to limited diagnostic capabilities may lead to poor outcomes. Therefore, the identification of COVID-19 patients most at risk of CAPA is crucial. It is also essential to recognise those CAPA patients who are likely to have a poorer outcome and may require more aggressive management approaches. Therefore, we performed a case–control study to identify risk factors and outcomes for CAPA in hospitalised patients with moderate to critical COVID-19 at a tertiary care centre in Karachi, Pakistan.

2 | METHODS

An unmatched case–control study was conducted on adult patients of age ≥ 18 years, hospitalised with COVID-19 from March 2020 to July 2021. The study was conducted at the Aga Khan University Hospital, Karachi, Pakistan, which is a 700 bedded, Joint Commission International accredited tertiary care centre. COVID-19 severity of illness was classified as moderate, severe or critical, based on World Health Organization (WHO) clinical classification.[7]

Cases were COVID-19 patients with CAPA, diagnosed using the 2020 European Confederation of Medical Mycology/International Society for Human and Animal Mycology consensus criteria.[8] These criteria require the presence of clinical signs and symptoms, abnormal lung imaging (pulmonary infiltrate or cavitating infiltrate or both) and microbiologic evidence of aspergillosis such as a respiratory specimen culture (bronchoalveolar lavage [BAL], tracheal aspirate or sputum) growing an *Aspergillus* spp. or a positive serum or lower respiratory sample galactomannan index (GMI) of more than 0.5 and 1.0, respectively. Cases were further classified into proven, probable and possible CAPA.[8] Controls were defined as patients hospitalised with moderate, severe or critical COVID-19 without CAPA.

All patients admitted with COVID-19 were consecutively recruited, and their medical records were reviewed to see if they fulfilled the eligibility criteria for cases. Sample size was calculated keeping two-sided confidence level(1-alpha) 95, power 80%, ratio of controls to cases 2:1, hypothetical proportion of controls with exposure 30% and least extreme odds ratio to be detected of 2.00[1]; a sample size of 104 cases and 207 controls was obtained which was inflated by 10 per cent. Patients were deemed to be colonised with *Aspergillus* spp. if they had *Aspergillus* species isolated from respiratory specimens but did not meet the criteria for proven, probable or possible CAPA. Patients with colonisation were excluded.[8] Descriptive data were obtained by reviewing the patient's in-hospital medical record charts. Information on patient characteristics such as age, sex, co-morbid conditions and severity of illness was collected on a pre-structured proforma. The study received ethics approval from the Aga Khan University ethics review committee (Reference No: 2020-5253-11575). No personal identifiers were collected, and information was stored in password-protected computers with access to primary investigator and relevant research personnel.

2.1 | Laboratory methods

Nasopharyngeal swabs were processed for detection of the SARS-CoV-2 virus by real-time reverse transcriptase polymerase chain reaction Cobas® SARS-CoV-2 Qualitative assay for use on the Cobas® 6800/8800 Systems (Roche Molecular Systems). *Aspergillus* species were isolated from the clinical specimen using standard culture methodology. Isolates were identified based on the colony and microscopic morphology. GMI was determined using Platelia *Aspergillus*®, (Bio-Rad Laboratories, Marnes-la-Coquette, France). Beta-D-Glucan was performed using (Fungitell®, Associates of Cape Cod).

2.2 | Statistical Analysis

Descriptive analysis was performed, and median and interquartile range (IQR) were reported for continuous variables such as age and length of stay and frequencies (percentages) for categorical variables like sex and co-morbid conditions. Bivariable and multivariable logistic regression analyses were performed after checking for multicollinearity, and odds ratios were calculated for various exposure-related variables. All variables with p-value of ≤ .1 on univariate analysis were included in multivariable analysis. The significance of each independent variable in the multivariable analysis was assessed by its p-value and likelihood ratio testing. Confidence intervals at 95% were calculated, and p-values of <.05 were considered statistically significant. Confounding was assessed by change in estimate of coefficient by 15 per cent. After developing the main effect model, the significance of all biologically plausible interactions was evaluated for inclusion in the multivariable model. Statistical analysis was conducted using STATA version 14.2.

3 | RESULTS

Between March 2020 and June 2021, 100 cases and 237 controls were identified. Out of 100 patients with CAPA, 27 were classified as having probable CAPA while 73 met the criteria for possible CAPA. No cases met the definition for proven CAPA. *Aspergillus* species were isolated from lower respiratory specimens of 96 cases, and 15 had septate hyphae on smear examination. More than one species of *Aspergillus* was identified in 16 patients. The most commonly isolated *Aspergillus* species were *Aspergillus flavus* in 76,

TABLE 1 Comparison of hospitalised COVID-19 patients who developed CAPA with patients who did not

Variables	CAPA (*n* = 100)	No CAPA (*n* = 237)	Unadjusted OR (95% CI)	*p*-Value
Median Age (IQR) years	65 (54–71.5)	55 (44–65)	1.04 (1.02–1.06)	<.001
Age Range *n* (%)				<.001
18–29	0 (0.0)	16 (6.75)		
30–49	13 (13.1)	69 (29.1)		
50–69	58 (58.5)	115 (48.5)		
> = 70	28 (28.2)	37 (15.6)		
Sex *n* (%)				.375
Male	72 (72.0)	159 (67.0)		
Female	28 (28.0)	78 (32.9)		
Symptoms *n* (%)				
Cough	40 (40.0)	151 (63.7)	0.38 (0.23–0.61)	<.001
Fever	53 (53.0)	189 (79.7)	0.28 (0.17–0.47)	<.001
Shortness of breath	61 (61.0)	160 (67.8)		.230
Severity of illness *n* (%)				<.001
Moderate	7 (7.0)	70 (29.5)	1 (Ref)	
Severe	4 (4.0)	31 (13.0)	1.29 (0.35–4.7)	
Critical	89 (89.0)	136 (57.3)	6.54 (2.8–14.8)	
Co-morbid				
DM	52 (52.0)	99 (41.7)		.085
HTN	56 (56.0)	112 (47.2)		.120
IHD	24 (24.0)	29 (12.2)	2.26 (1.24–4.13)	.008
CKD	19 (19.0)	9 (3.8)	5.94 (2.58–13.6)	<.001
CLD	6 (6.0)	2 (0.8)	7.5 (1.48–37.8)	.015
CVA	9 (9.0)	4 (1.6)	5.76 (1.73–19.17)	.004
Malignancy	4 (4.0)	8 (3.4)		.755
Haematological disease	8 (8.0)	0 (0.0)		<.001
Respiratory disorders				
Asthma	10 (10.0)	14 (5.9)		.182
COPD	6 (6.0)	2 (0.8)	7.5 (1.48–37.8)	.010
Bronchiectasis	2 (2.0)	0 (0.0)		.087
ILD	4 (4.0)	0 (0.0)		.007
Imaging				
Bilateral patchy infiltrates	88 (88.0)	94 (39.7)	11.15 (5.78–21.51)	<.001
Consolidation	33 (33.0)	12 (5.1)	9.23 (4.51–18.8)	<.001
Cavitation	4 (4.0)	0 (0.0)		
Medications *n* (%)				
Tocilizumab	37 (37.0)	72 (37.0)		.990
Steroids	100 (100.0)	108 (65.4)		<.001
Invasive mechanical ventilation *n* (%)	56 (56.0)	40 (16.9)	6.26 (3.72–10.55)	<.001

Abbreviations: CLD, chronic liver disease; COPD, chronic obstructive pulmonary disease, CVA, cerebrovascular accident; IHD, ischemic heart disease; ILD, interstitial lung disease.

followed by *Aspergillus niger* in 37 and *Aspergillus fumigatus* in 20 patients. The median Beta-D-glucan level was 225 (IQR: 114–523) for patients with probable CAPA and 19.4 (IQR 7.8–77) for patients with possible CAPA. Furthermore, the median GMI was 1.75 (IQR 1.07–4.03) for patients with probable CAPA, whereas this was 0.154 (IQR 0.126–0.20) for patients with possible CAPA. Of the 100 cases, 89 received antifungal treatment: most often with voriconazole in 82 patients, followed by amphotericin B deoxycholate (deoxAMB) in 33 patients. Those patients who were rapidly deteriorating with septic shock or those who had significant liver dysfunction were empirically started on deoxAMB, and it was changed to voriconazole once culture for *Aspergillus* spp. or GMI ≥ 0.5 had been reported or when liver enzymes had improved. In most cases when amphotericin was used, this was later changed to voriconazole as step-down treatment. The duration of treatment with antifungals ranged from 2 to 4 weeks. The 11 cases who did not receive therapy, either had a rapid deterioration and died before the cultures were reported, or care had been withdrawn and home-based palliative care initiated.

The overall median age of cases was 10 years older than the controls (65 vs. 55 years) while both groups had a male predominance (p-value = .375) (Table 1). In comparison to the controls, fewer cases reported cough (40% vs. 64%) and fever (53% vs. 80%) on presentation. The most frequent co-morbid conditions were diabetes mellitus and hypertension in both groups. Most of the cases had critical COVID at presentation compared to controls (89% vs. 57%). A greater proportion of cases had received systemic steroids compared to controls (100% vs. 65%) (p-value < .001) and had required invasive mechanical ventilation (56% vs. 17%, OR = 6.26; 96% CI 3.72–10.5, p-value < .001) (Table 1). In multivariate analysis, the risk factors found to be independently associated with CAPA included age greater than or equal to 60 years at presentation, critical illness at presentation and underlying co-morbid of chronic kidney disease (CKD) (Table 2). Patients with CAPA were 6.4 times more likely to die compared to those without CAPA (95% CI 3.6–11), and their median length of hospital stay was longer (14 days vs. 6 days). Moreover, patients with CAPA had a significantly greater proportion of complications including acute respiratory distress syndrome, septic shock, nosocomial infections, pneumothorax, non-ST elevation mycocardial infarction (NSTEMI), and acute kidney injury compared to controls (Table 3). Multivariable logistic regression analysis was performed to determine independent predictors of mortality, and it was found that patients hospitalised with COVID-19 with age ≥ 60 years (aOR 2.19; 95% CI: 1.23–3.90); critical disease at presentation (aOR 5.35; 95% CI: 1.82–15.77); and complications including pneumothorax (aOR 2.19; 95% CI: 1.23–3.90), NSTEMI (aOR 2.19; 95% CI: 1.23–3.90) and CAPA (aOR 2.19; 95% CI: 1.23–3.90) had greater odds of death after adjusting for confounding and interactions with other variables (Table 4).

TABLE 2 Multivariable logistic regression analysis for risk factors for CAPA

Variables	Odds ratio	p-Value	95% Confidence interval
Age			
<60 years	Ref		
≥60 years	2.0	.008	1.20–3.35
Severity of illness			
Moderate	1 (Ref)		
Severe	1.09	.889	0.29–4.11
Critical	5.04	<.001	2.18–11.63
Chronic kidney disease	3.78	.003	1.57–9.08

4 | DISCUSSION

In our centre, compared to patients with COVID-19 who do not develop CAPA, we found that age ≥ 60 years, CKD and a critical disease at presentation were independent risk factors for the development of CAPA. Mortality was six times higher in the patients with CAPA as compared to controls. To date, CAPA has been variably reported from different parts of the world. However, risk factors for CAPA remain to be elaborated particularly from LMICs in view of epidemiological differences between COVID-19 severity as well as environmental differences which influence *Aspergillus* isolation.[3,9,10] Our study serves to fill this important gap in the literature.

According to a systematic review and metanalysis of observational studies, the majority of which were from European countries, CAPA was found to be associated with older age and the presence of chronic obstructive pulmonary disease as co-morbid and subsequently led to greater mortality and ICU admission.[11] Recent studies from Spain (28 CAPA patients)[12] and Brazil (14 CAPA patients) found association with older age which is consistent with the finding from our study. Among co-morbid conditions, studies from Korea[13] and Spain[12] found an association with chronic lung disease. Furthermore, a study from Spain[12] has also described CKD to be an independent risk factor, also similar to our study.

Among risk factors for CAPA, we found an independent association with critical COVID-19 at presentation (89% vs. 57%), particularly those requiring invasive mechanical ventilation (56%). This was similarly reported from study done in Turkey.[14] Findings from a multicentre study from Korea reported significant association between critical COVID-19 and mechanical ventilation with CAPA on univariate analysis but was not found to be predictive of CAPA.[15] A French multicentre study reported no association of probable IPA with severity of COVID-19 at presentation as well as mechanical ventilation when compared to patients without IPA in ICU setting. However, they used lab parameters rather than WHO clinical definition of severity.[16] A recently published systematic review and meta-analysis reported that based on sequential organ failure assessment score, CAPA patients had comparatively greater severity of illness at presentation.[17] Most studies exploring CAPA risk factors have either included all intubated patients or critically ill patients, hence excluding possibility of analysing this as a risk factor for CAPA.[18,19]

TABLE 3 Comparison of outcomes of hospitalised COVID-19 patients who developed CAPA with patients who did not

Variables	CAPA ($n = 100$)	No CAPA ($n = 237$)	Unadjusted OR (95% CI)	*p*-Value
Complications *n* (%)				
ARDS	74 (74.0)	66 (27.8)	7.37 (4.34–12.5)	<.001
Septic shock	65 (65.0)	10 (4.2)	42.15 (19.8–89.6)	<.001
Nosocomial infection	43 (43.0)	9 (3.8)	19.11 (8.1–41.4)	<.001
Pneumothorax	17 (17.0)	8 (3.3)	5.86 (2.43–14.09)	<.001
NSTEMI	29 (29.0)	18 (7.6)	4.96 (2.60–9.48)	<.001
AKI	61 (61.0)	10 (4.3)	35.19 (16.6–74.5)	<.001
Outcome *n* (%)				<.001
Discharged	45 (45.0)	191 (80.5)	1 (Ref)	
Died	48 (48.0)	32 (13.5)	6.36 (3.6–11.0)	
LAMA	7 (7.0)	14 (5.9)	2.07 (0.8–5.4)	
Median LOS (IQR)	14 (8–20.5)	6 (4–10)	1.12 (1.08–1.17)	<.001

Abbreviations: AKI, acute kidney injury; ARDS, acute respiratory distress syndrome; LAMA, left against medical advice; LOS, length of stay; NSTEMI, non-ST-elevation myocardial infarction.

Studies have variably shown association of COVID-19 treatments with CAPA. Dellière et al.[16] did not find dexamethasone to be significantly associated with CAPA despite observing a trend(11.5 vs. 28.6%, $p = .08$) but interestingly found an association with Azithromycin treatment of ≥3 days (odds ratio 3.1, 95% CI: 1.1–8.5, $p = .02$). A large multicentre multinational cohort study did not find an association with corticosteroids or azithromycin but found an association with administration of Tocilizumab.[1] In our study, we found CAPA to be significantly associated with steroid treatment in univariate analysis but no association with Tocilizumab. However, we had not collected data on azithromycin treatment in our cohort.

The most common species causing CAPA in our centre was *Aspergillus flavus*, followed by *A. niger* and then *A. fumigatus*. Although this distribution is quite different from that reported from the rest of the world, where *A. fumigatus* is the most common invasive aspergillus species,[20] *A. flavus* is the most common species reported from Karachi, Pakistan, in a wide spectrum of aspergillosis[4,21,22] as well as the environment.[23]

TABLE 4 Multivariable logistic regression analysis for risk factors for mortality

Variables	Odds ratio	*p*-Value	95% Confidence interval
Age			
<60 years	Ref		
≥60 years	2.19	.007	1.23–3.90
Severity of illness			
Moderate	1 (Ref)		
Severe	1.73	.469	0.39–7.67
Critical	5.35	.002	1.82–15.77
Non-ST-elevation MI	4.49	<.001	2.10–9.59
Pneumothorax	5.96	.001	1.98–17.91
COVID-19-associated pulmonary aspergillosis	2.10	.015	1.15–3.83

Mortality in patients with CAPA was 48%, and it was significantly higher compared to those patients without CAPA (13%). This has been similarly reported from Europe (58% vs.24.1%), Turkey (ICU mortality of 67.4% vs. 29.4%)[14] as well as systematic reviews of studies largely conducted in high-income countries.[17,20,24,25] However, despite higher mortality with CAPA in COVID-19 patients in Brazil, no significant difference was observed in comparison with non-CAPA patients.[19]

To the best of our knowledge, our study is the one of the few and the largest from LMICs, from an area with a high fungal disease burden with limited resources for diagnosis.[26] Moreover, our study evaluated the impact of CAPA on patient outcomes. Our study had certain limitations including the fact that this is a single-centre study although our centre is a major tertiary care centre with a dedicated COVID-19 unit and receives referrals from across the country owing to capability and expertise for diagnosing fungal infections. Furthermore, a number of patients were included prior to vaccination roll-out in the country which may change the predisposition to CAPA. Another limitation could be non-availability of BAL for GM detection since bronchoscopies were not performed and serum GM was negative in many patients; therefore, some of the possible cases may actually be probable. Our study was also not powered for survival analysis, but we did find an independent association of mortality with CAPA. Future studies from Pakistan may help confirm this finding.

5 | CONCLUSION

We conclude that patients with age greater than 60 years, CKD and critical illness at presentation are at greater risk for CAPA. Moreover, mortality and risk of other complications are higher. Hence, we recommend a high index of suspicion for CAPA presenting with these

risk factors for early initiation of antifungal therapy in order to avoid an adverse outcome.

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CONFLICT OF INTEREST

None of the authors have any conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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