Original Article

Post-COVID pulmonary fungal infections: An unanticipated predicament or a ticking time bomb? Clinico-microbiological profile of cases encountered during the second wave of COVID-19 pandemic at a teaching hospital in the Himalayas with a brief literature review

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Abstract

Introduction: This study attempts to generate preliminary data regarding post-COVID pulmonary fungal infections, namely, COVID-19-associated pulmonary aspergillosis (CAPA), COVID-19-associated pulmonary mucormycosis (CAPM), and mixed infections from the Himalayas and compares the micro-radio-clinical profile and outcomes of the affected patients. **Materials and Methods:** A retrospective data analysis was conducted, where clinical profiles, microbiological and radiological reports, and outcomes of $n = 16$ patients of post-COVID pulmonary infections were compared. **Results:** Of $n = 16$ patients, $n = 7$ had CAPA ($n = 5$ *Aspergillus fumigatus*, $n = 1$ *Aspergillus flavus, and* $n = 1$ *Aspergillus niger*), $n = 5$ CAPM (Rhizopus arrhizus), and $n = 4$ with mixed infections ($n = 3$ infected with *Aspergillus fumigatus* and *Rhizopus* spp. and $n = 1$ with *Aspergillus flavus* and *Rhizopus arrhizus*). Thick-walled cavitary lesions, air–fluid levels, and multiple centrilobular nodules were some of the common radiological findings reported among these patients. **Conclusion:** The immuno-compromised state following COVID-19 infection and treatment might be responsible for the progression of regular exposure to the dense Himalayan vegetation into an invasive pulmonary fungal infection. Suspecting post-COVID pulmonary fungal infection is necessary for primary care physicians to ensure timely referral to higher centers. Mixed pulmonary fungal infections (coinfection with *Aspergillus* spp. and *Rhizopus* spp.) are also emerging as important sequelae of COVID-19.

Keywords: COVID-19, COVID-19-associated pulmonary aspergillosis (CAPA), COVID-19-associated pulmonary mucormycosis (CAPM), mixed pulmonary fungal infection

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Received: 28-06-2023 **Revised:** 08-08-2023
Accepted: 09-08-2023 **Published:** 21-12-2023

Access this article online

Quick Response Code:

Website: http://journals.lww.com/JFMPC

DOI: 10.4103/jfmpc.jfmpc_1073_23

How to cite this article: Puri O, Bhatia M, Rekha US, Chakraborty D, Dua R, Dhar M, *et al*. Post-COVID pulmonary fungal infections: An unanticipated predicament or a ticking time bomb? Clinico-microbiological profile of cases encountered during the second wave of COVID-19 pandemic at a teaching hospital in the Himalayas with a brief literature review. J Family Med Prim Care 2023;12:3228-35.

Introduction

The global spread of COVID-19 over the past two years shifted the focus of medical research toward understanding the microbiology, epidemiology, vaccination, and treatment of the infection.[1] While much is known about the infection itself, newer complications associated with it and the therapeutic agents used in its treatment are still being reported.[2] Fungal coinfections and post-COVID fungal sequelae as complications of COVID-19 created a lot of havoc among the general population and healthcare professionals alike.[2] Post-COVID fungal infections have been reported to affect various organ systems, including but not limited to the brain, orbits, sinuses, oral cavity, lungs, and blood.[3-7] A variety of fungi have been identified as the causative pathogens of these post-COVID sequelae around the world, such as *Aspergillus, Rhizopus, Candida, Pneumocystis, Fusarium,* and *Scedosporium/Lomentospora* spp.[7] While *Aspergillus* spp. is known to cause post-COVID pulmonary fungal infection, i.e., COVID-19-associated pulmonary aspergillosis (CAPA)—a form of invasive pulmonary aspergillosis, *Rhizopus* spp. most commonly causes rhino-orbito-cerebral mucormycosis, *Candida* spp. infections most commonly present as Candidemia, *Pneumocystis* spp. as Pneumonia, and non-Aspergillus molds as coinfections along with COVID-19.[7,8]

It has also been reported that in regions where mycoses are prevalent, COVID-19 infection and immunosuppressive therapy used in its treatment may result in the reactivation of dormant past infections.[7] The Himalayan region has very dense vegetation and diverse flora; hence, the prevalence of mycoses is higher in this region of the country.[9] Furthermore, a majority of households in the hilly terrain of the state use self-harvested biomass as their domestic fuel, increasing their exposure to potentially pathogenic fungal elements. There is limited literature reporting fungal exposure and latent/active infection from the Himalayas. The most recent (2010) evidence from this region reports the point prevalence of fungal colonization among patients with chronic pulmonary conditions to be 50%.[10] While post-COVID exposure to pathogenic fungal strains may be one reason for post-COVID fungal infections, the possibility of reactivation of latent exposures following immunosuppression due to COVID-19 or steroid therapy is also likely. Such opportunistic invasive fungal infections have been reported to follow other respiratory viral illnesses such as *Influenza* and *Parainfluenza* as well[7,8] which further emphasizes the need of studying fungal infections following respiratory viral infections, especially in a region like the Himalayas, where a majority of the population is exposed to such fungi on a day-to-day basis.

The Himalayas happen to be a difficult terrain for establishing elaborate healthcare institutions. Hence, primary care centers and physicians are mainly responsible to deliver healthcare high up the hills, and deep within the valleys. This further necessitates the generation of epidemiological data on the relatively unexplored and also recently spreading infections, from this region. Hence, the current study characterizes post-COVID pulmonary fungal infections to educate primary care physicians in the periphery regarding the data regarding the clinico-microbiological profile of post-COVID pulmonary fungal infections and their outcomes in this region. Among pulmonary fungal infections following COVID-19, CAPA emerged as the most prevalent infection worldwide, followed by COVID-19-associated pulmonary mucormycosis (CAPM).[7,11] A recent review on post-COVID pulmonary fungal infection highlights the gaps in the understanding of these invasive fungal sequelae of COVID-19.[8] The understanding of CAPM is further limited by its limited prevalence relative to CAPA.[8] Furthermore, to the best of our knowledge, the profile of post-COVID fungal infection patients is yet to be reported from the Himalayan region. Thus, the study attempts to compare the micro-radio-clinical profiles of patients diagnosed with post-COVID pulmonary fungal infections highlighting similarities and dissimilarities between these two invasive fungal infections following COVID-19.

Materials and Methods

A retrospective study was conducted with due Ethical Clearance from the Institutional Ethical Committee (Regd No—EC/NEW/Inst/2020/1046) received via Letter No.—AIIMS/IEC/22/356 Dated—18/08/2022, at a teaching hospital in Uttarakhand, India. The objectives of this study were:

(1) To generate preliminary data on the post-COVID pulmonary fungal infection from a teaching hospital in the Himalayas.
(2) To compare the underlying risk factors, clinical symptoms, micro-radio-clinical profile, and outcomes of patients suffering from pulmonary fungal infection following COVID-19.

Inclusion criteria

In-patients diagnosed with pulmonary fungal infection following COVID-19. Case Definitions:

1. COVID-19-associated pulmonary mucormycosis (CAPM)—Patients diagnosed to have pulmonary mucormycosis at the same time or within three months of suffering from COVID-19 were included as CAPM cases.[12] A diagnosis of pulmonary mucormycosis was confirmed if broad aseptate hyphae were seen on KOH mount microscopy [Figure 1] or *Rhizopus* spp. was cultivated on SDA culture from the patients' sputum, endotracheal tube (ET), or bronchoalveolar lavage (BAL).
2. COVID-19-associated pulmonary aspergillosis (CAPA)—Patients diagnosed to have pulmonary aspergillosis at the same time or within three months of suffering from COVID-19 were included as CAPA cases.[12] A diagnosis of pulmonary aspergillosis was confirmed if thin septate hyaline hyphae were seen on KOH mount or Gram stain microscopy [Figure 2] or *Aspergillus* spp. was cultivated on SDA culture from the patients' sputum, endotracheal tube (ET), or bronchoalveolar lavage (BAL).
3. Mixed infection—Patients' sputum, endotracheal tube (ET), or bronchoalveolar lavage (BAL) reported more than one fungi were classified [Figure 3] based on the dual infection diagnosis algorithm postulated by Muthu *et al.*[12]

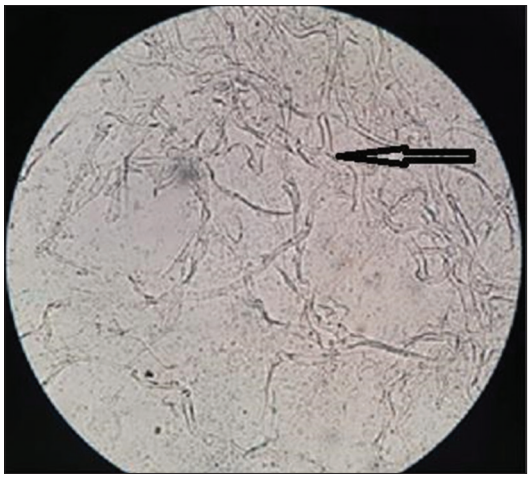

Figure 1: KOH Mount of lower respiratory tract sample of a patient showing hyaline broad aseptate and pauciseptate hyphae suggestive of *Rhizopus* spp

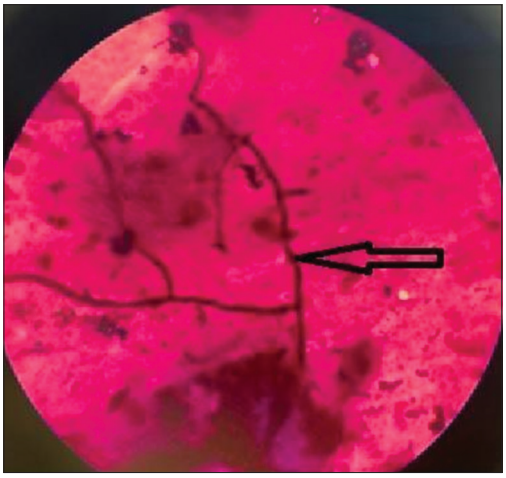

Figure 2: Gram-stained smear of a lower respiratory tract sample of a patient showing acute angle branching suggestive of *Aspergillus* spp

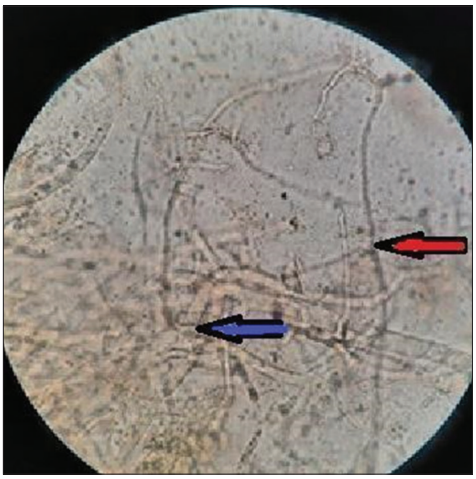

Figure 3: KOH Mount of a lower respiratory tract sample of a patient showing hyaline aseptate hyphae (blue arrow) and thin hyaline septate hyphae (red arrow) suggestive of mixed infection caused by *Rhizopus* spp. and *Aspergillus* spp., respectively

Exclusion criteria

Patients presenting with pulmonary aspergillosis or mucormycosis with an unknown COVID status were excluded.

Sputum, endotracheal tube (ET), and bronchoalveolar lavage (BAL) samples of patients admitted to the inpatient departments in the query of pulmonary mucormycosis and/or aspergillosis following COVID-19 were sent to the microbiology laboratory for examination and were subjected to preliminary KOH microscopic examination. This was followed by the inoculation of these samples on Sabouraud dextrose agar plates. The inoculated culture media were subjected to aerobic incubation at 37 degrees Celsius, and observations were recorded per standard microbiological guidelines. A record of the patient's symptoms, diagnosis, and the report of their microbiological, biochemical, and radiological investigations done for the patients diagnosed with pulmonary fungal infections following COVID-19 were collected from the hospital database. The following outcomes were considered indicators for the study's results:

1. The patient's clinical symptoms, comorbid conditions, diagnosis, and outcome.
2. Microbial profile of respiratory samples collected from the patients.
3. Radiological profile of the included patients.

Results

Data of n = 16 patients with a history of pulmonary fungal infections following COVID-19 admitted to the hospital between May and September 2021 were extracted. The mean age of the patients included was 53 ± 13.38 years. Of a total of n = 16 patients, n = 7 were diagnosed with pulmonary aspergillosis (n = 5 were infected with *Aspergillus fumigatus*, n = 1 with *Aspergillus flavus,* and n = 1 with *Aspergillus niger*), n = 5 were diagnosed with pulmonary mucormycosis infected with *Rhizopus arrhizus,* and n = 4 were diagnosed with mixed pulmonary fungal infections (n = 3 infected with *Aspergillus fumigatus* and *Rhizopus arrhizus* and n = 1 with *Aspergillus flavus* and *Rhizopus arrhizus*, respectively). The clinical and microbiological profiles of the patients are summarized in Tables 1 and 2.

Pulmonary radiological investigation of only 8 of the included 16 patients was available, of which n = 5 had CAPA, n = 1 had CAPM, and n = 2 had mixed infection. Among n = 5 patients of CAPA, n = 1 had a close to normal CECT thorax, 2 had bilateral lung involvement, and 2 had only one lung affected. The patient with CAPM has a well-formed lung abscess, while those with mixed infection also had unilateral lung involvement. All 4 of the CAPA and one patient with a mixed infection, having pathological CECT findings, had typical thick-walled cavitary lesions with air–fluid levels and multiple centrilobular nodules, giving a tree-in-bud appearance suggestive of an infective etiology most likely fungal. [Figures 4 and 5]. N =1 patient of mixed infection reported cavitary fungal pneumonia on X-ray.

Table 1: Demographic, clinical profile, and outcome of patients suffering from pulmonary fungal infections following COVID-19

Patient characteristic	Pulmonary aspergillosis		Pulmonary mucormycosis		Mixed infection		Total	
	n=7	%	*n*=5	%	*n*=4	%	*n*=16	%
Demographics								
Males	5	71.43	3	60	4	100	12	75
Females	2	28.57	2	40	0	-	4	25
Mean age (years) ± S.D.	48.57±11.47	-	58±17.22	-	55.5±11.9	-	53±13.38	-
Clinical symptoms								
Fever	5	71.43	4	80	3	75	12	75
Dyspnea	6	85.71	5	100	2	50	13	81.25
Chest pain	0	-	1	20	0	-	1	6.25
Cough	2	28.57	2	40	2	50	6	37.5
Expectoration	2	28.57	1	20	0	-	3	18.75
Hemoptysis	2	28.57	0	-	0	-	2	12.5
Generalized weakness	1	14.28	0	-	1	25	2	12.5
Comorbid conditions								
Diabetes	4	57.14	3	60	2	50	9	56.25
PTB	2	28.57	2	40	0	-	4	25
AKI	1	14.28	3	60	0	-	4	25
CKD/CLD/COPD/CAD	1	14.28	2	40	0	-	3	18.75
Hypertension	1	14.28	1	20	1	25	3	18.75
End organ damage	2	28.57	5	100	1	25	8	50
Treatment requirements								
Requirement of supplemental oxygen	7	100	5	100	2	50	14	87.5
High flow oxygen	4	57.14	3	60	2	50	9	56.25
Steroids	2	28.57	1	20	0	-	3	18.75
Outcome								
Death	4	57.14	3	60	0	-	7	43.75
Alive	2	28.57	1	20	3	75	6	37.5
LAMA	1	14.28	1	20	1	25	3	18.75

PTB=Pulmonary tuberculosis, AKI=Acute kidney injury, CKD=Chronic kidney disease, CLD=Chronic liver disease, COPD=Chronic obstructive pulmonary disease, CAD=Coronary artery disease, LAMA=Leave against medical advice

Table 2: Microbiological profile of patients suffering from mixed pulmonary fungal infections following COVID-19

Pt. No.	KOH Mount findings	Fungal culture findings	Diagnosis as per Muthu *et al*
1.	Broad aseptate hyphae (suggestive of *Rhizopus* spp.)	*Aspergillus fumigatus*	Proven CAPM with proven CAPA
2.	Broad aseptate hyphae (suggestive of *Rhizopus* spp.) and thin septate hyaline hyphae (suggestive of *Aspergillus* spp.)	*Aspergillus fumigatus*	Proven CAPM with proven CAPA
3.	Broad aseptate hyphae (suggestive of *Rhizopus* spp.)	*Aspergillus flavus* and *Rhizopus arrhizus*	Proven CAPM with proven CAPA
4.	Broad aseptate hyphae (suggestive of *Rhizopus* spp.)	*Aspergillus fumigatus*	Proven CAPM with proven CAPA

A few patients also reported architectural disorientation, traction bronchiectasis, and fibrotic changes.

Discussion

Post-COVID patients have several risk factors that predispose them to contracting fungal infections. Immunosuppression associated with the infection is one of the most well-studied risk factors, although a lot is yet to be explored.[13] There have been a variety of studies reporting dysfunction of various immune cells such as CD3+ Helper T cells, CD4+ Helper and Cytotoxic T cells, CD8+ Cytotoxic T cells, Regulatory T cells, Memory T cells and B cells underlying immunosuppression in COVID-19.[13-22] While peripheral sequestration of immune cells has been hypothesized as one of the mechanisms responsible for this immune dysfunction, absolute cellular dysregulation due to repeated viral attacks has also been reported by some studies.[13]

Along with immunosuppression, underlying chronic comorbidities such as diabetes and cancers and post-transplant immunosuppressive therapy have also been postulated to increase the risk of post-COVID fungal sequelae.[23-25] This might be attributed to the comorbid immuno-compromised state of the patient due to the chronic illness as well as to the relatively severe infection caused by the coronavirus among these patients. Other risk factors postulated to contribute toward post-COVID fungal sequelae are immunosuppressive steroid therapy and high-flow oxygen used to treat COVID-19, especially in those patients with severe disease.[24,26] Apart from general risk factors hypothesized to underlie post-COVID fungal sequelae, daily exposure to dense vegetation

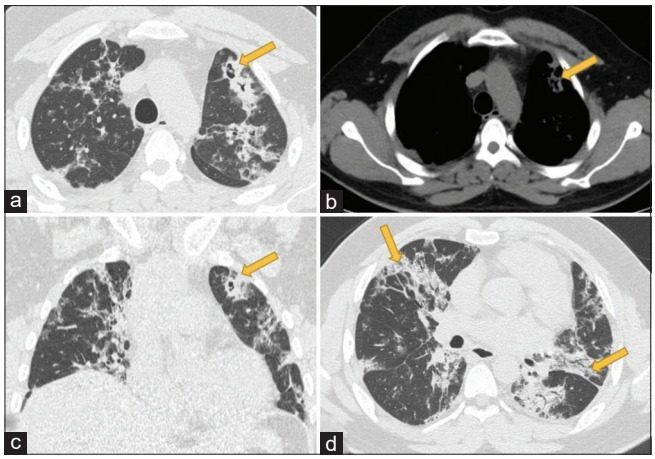

Figure 4: Axial lung and mediastinal window and coronal lung window scans of the chest (a-c) showing a thin-walled cavity with internal contents along with surrounding ground-glass attenuation along the wall of the cavity. Axial lung window scans (d) displaying extensive COVID-related changes in the form of consolidation admixed with fibrotic changes. The presence of a cavity with internal contents and surrounding ground-glass attenuation is highly suggestive of invasive fungal infection

and diverse flora of the Himalayan region might be attributed to invasive pulmonary fungal infections following COVID-19 and the diversity of etiological pathogens identified through this study.

Pulmonary fungal coinfections and post-COVID fungal sequelae have been reported to poorly affect the outcome of patients suffering from COVID-19.[25,27] With the increasing prevalence of COVID-19 infection, it has become imperative to understand these fungal sequelae in terms of their predisposing risk factors, clinico-micro-radiological profile, treatment requirements, and patient outcomes. Reporting the clinical and epidemiological data on these fungal sequelae in a region like the Himalayas is even more important. Primary care physicians happen to be the only healthcare providers in the Himalayan heights and seldom have access to sophisticated diagnostic techniques. Hence, they must be made aware of the epidemiology and clinical profile of recently spreading detrimental clinical conditions to facilitate timely referral.

While CAPA and CAPM are common post-COVID pulmonary fungal infections, more studies have reported, discussed, and analyzed CAPA, probably due to a disproportionately higher prevalence of CAPA compared to CAPM or mixed infections.[7,25,28] Contrary to the available literature, the current study reports 43.75% of all post-COVID pulmonary infections to be CAPA, 31.25% CAPM, and 25% mixed infections. While it is difficult to hypothesize an explanation for the high prevalence of CAPM and mixed infections taken together (56.25%), it might be attributable to the rich vegetation and dense flora of the Himalayas surrounding the healthcare facility. While the population of the state is regularly exposed to these fungal species more than other regions of the country, the immuno-compromised state following COVID-19 infection might be responsible for the rapid progression of these exposures to invasive pulmonary stages.[7]

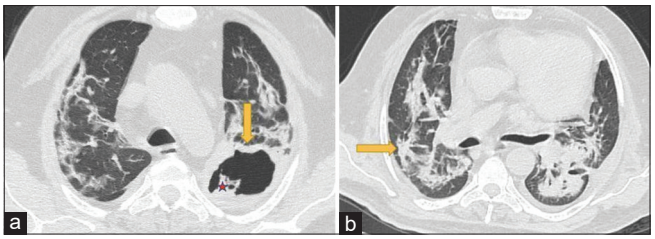

Figure 5: Axial lung window of chest displaying well-defined thin-walled cavity in the superior segment of left lower lobe (arrow in a) with internal debris-like contents (star in a). COVID-related changes are seen as retracting bands of fibrosis admixed with areas of consolidation (arrow in b). The presence of a cavity with internal contents is highly suggestive of superadded fungal infection

Owing to the limited number of post-COVID pulmonary infection cases diagnosed during the study period, it is difficult to reliably characterize the differences between CAPA and CAPM. Some notable differences between the clinical profiles of patients presenting with CAPA/CAPM were observed and have been discussed here. The proportion of most clinical symptoms was reported to be similar across patients presenting with either of the two infections.[12] Hemoptysis was reported only among patients later identified as suffering from CAPA (n = 2, 28.57%), unlike among none of the patients with CAPM. While the current study reported several differences among the predisposing comorbidities across the two groups, the prevalence of diabetes was reported to be similar across both the groups, unlike the Delphi consensus statement from the Fungal Infection Study Forum (FISF) and Academy of Pulmonary Sciences (APS), India, which reported diabetes to be more commonly associated with CAPM than with CAPA.[29-31] A notable difference observed between the prevalence of end-organ damage between the two groups of patients was that all patients suffering from CAPM had end-organ damage, but only n = 2 (29%) of those diagnosed with CAPA had the complications above. Similarly, the prevalence of acute kidney injury or chronic illnesses like CKD, CLD, COPD, and CAD was also relatively more among patients diagnosed with CAPM. This suggests that COVID-19 patients with pre-existing chronic comorbidities are relatively more predisposed to contracting pulmonary mucormycosis when compared to pulmonary aspergillosis. While there is a paucity of evidence suggesting this predisposition to CAPM over CAPA in the setting of chronic comorbidities, the Delphi consensus does suggest that diabetes predisposes to CAPM more than it does to CAPA.[29-31] On the contrary, the treatment requirement and clinical outcomes of patients infected with either mold were similar.

While a handful of cases of mixed pulmonary fungal infections have been reported among COVID-19 patients, the proportion of the same in the current study was as high as 25%. It has been hypothesized that the prevalence of mixed infection is higher and is being under-reported since both species are not identified on microscopy/grown on culture simultaneously during the complete course of the infections and overlaps have been reported in the imaging findings of both infections.[28,32,33]

Microbiologically, three of four patients were infected with *Aspergillus fumigatus* and *Rhizopus arrhizus*, while one patient was infected with *Aspergillus flavus* and *Rhizopus arrhizus*. As per Muthu *et al.*'s classification of patients suffering from a mixed infection, all four patients had a proven CAPA and proven CAPM since two patients reported *Rhizopus arrhizus* on KOH microscopy and *Aspergillus fumigatus* was cultivated on SDA Agar culture.[12] Both *Aspergillus* spp. and *Rhizopus* spp. were identified from the KOH microscopy of the third patient, and *Aspergillus flavus* and *Rhizopus arrhizus* were cultivated simultaneously from the sample of the fourth patient.[12] A handful of cases of mixed pulmonary fungal infections have been reported in the past, with many reporting both species on microscopy and a few reporting growths of both on culture media.[32,34-37] This disparity between microscopy and culture findings could be attributed to the lack of technical expertise in diagnosing mixed fungal infections.

The clinical profile of patients suffering from mixed infection differed notably from those diagnosed with single-species pulmonary fungal infections. All the patients suffering from mixed infections were identified as males, consistent with the proportion of males contracting mixed infections being higher than females reported in the past.[32] Single species infections were also reported more in males than females, but the male/female ratio was 2:1, unlike an absolute male predominance in the case of mixed infection in our study. 20–40% of patients diagnosed with single-species infection complained of chest pain, expectoration, or hemoptysis, but none of the patients diagnosed with mixed infection had these complaints. Similarly, none of the patients diagnosed with mixed infection had a history of suffering from pulmonary tuberculosis, acute kidney injury, or any chronic comorbidities like CKD, CLD, COPD, and CAD. The presence of diabetes, hypertension, and end-organ damage was similar among patients with pulmonary aspergillosis and also reported to be present among patients who reported having a mixed infection in the past.[32]

Striking differences were noted in the treatment requirements and outcomes of patients with mixed infection and those with single-species infection. While there were no deaths, unlike about 60% mortality in cases of single-species infections, the survival rate was as high as 75%, unlike about 30% among the rest. Even more striking to observe was that only 50% of patients with mixed infections needed supplemental high-flow oxygen, unlike a 100% requirement among the other groups. None of the patients with mixed infection needed steroids in the course of their treatment, for high flow oxygen sufficed for their oxygen requirements. Unlike what would be expected from mixed infections, this pair of pulmonary fungal infections appears to occur among patients with lesser comorbidities, has a milder clinical course, and is a better prognostic factor compared to single-species infections. There is limited evidence to support this finding from the current study. Hence, the investigators suggest further research in this area to compare the clinical profile and outcomes of patients with mixed infection against patients suffering from single-species infection.

Lung abscess reported from the patient of CAPM is a sign suggestive of CAPM >CAPA/mixed infection as the pre-existing literature.[12] Past studies have reported centrilobular nodules or a tree-in-bud appearance to be nonspecific findings suggestive of CAPA or dual infections.[12] Consistent with the existing evidence, centrilobular nodules or a tree-in-bud appearance were reported from CECT of four out of five patients of CAPA and one of two patients of mixed infection whose radiological investigations were available. While the presence of air–fluid level is a relatively nonspecific sign, thick-walled cavities reported in these patients have been reported to be highly suggestive evidence of CAPA/mixed infection but more likely suggestive of CAPM.[12] In the current study, thick-walled cavities were seen only among CAPA and mixed infection patients, probably because the radiological investigation of CAPM patients was not available. Thus, evidence from this study is inconclusive regarding thick-walled cavities, a radiological sign for CAPM > CAPA. Fungal cavitary pneumonia has also been reported to be more likely suggestive of CAPM but was reported from only one patient of mixed infection in the current study.[12] Architectural disorientation, traction bronchiectasis, and fibrotic changes reported from the CECTs of several patients was a sign of past COVID infection having affected pulmonary parenchyma.

The limited sample size, convenience sampling, and retrospective analysis with missing clinical and radiological data points are some of the major limitations of this study that necessitate further exploration into the study's results before its conclusion can be practically applied. Moreover, structured data from multicentric studies might be more insightful to reliably compare the differences in the clinical, microbiology, and radiological profile of CAPA, CAPM, and mixed infection.

Conclusion

The immuno-compromised state following COVID-19 infection/treatment might be responsible for the progression of regular exposure to the dense Himalayan vegetation into an invasive pulmonary infection. Suspecting post-COVID pulmonary fungal infection is necessary for primary care physicians to ensure timely referral to higher centers. Along with CAPM and CAPA, mixed pulmonary fungal infections with *Rhizopus* and *Aspergillus* spp. are also emerging as important sequelae of COVID-19.

Financial support and sponsorship

The research was conducted at the All India Institute of Medical Sciences (AIIMS), Rishikesh, Uttarakhand, India. No financial support or grants were availed for the conduction of the study.

Conflicts of interest

There are no conflicts of interest.

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