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Computed Tomographic features of Pulmonary Mucormycosis among Covid 19 Survivors: A Diagnostic Challenge

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Abstract

Background and Aims: Moderate to severe corona virus-infected patients are usually managed by systemic steroids and immunosuppressant drugs, increasing the risk of opportunistic fungal infections. Pulmonary mucormycosis is a rare but fatal invasive fungal disease that mainly affects people with compromised immune systems and is associated with several diagnostic difficulties. This study sheds light on the diagnostic challenges and benefits of chest computed tomography in the early detection of mucormycosis lesions, which will help physicians and surgeons manage the disease more effectively.

Methods: Our study reports a single-center experience with pulmonary mucormycosis in recovered/active COVID-19 patients. We reviewed all medical records of COVID-19 positive patients diagnosed with pulmonary mucormycosis histopathologically. Chest CT images were extracted from the Picture Archiving and Communication System (PACS) and evaluated.

Results: Our study demonstrated reverse halo sign in the majority (75%) of patients during the early disease course. In addition to RHS, several other lesions like GGOs, peri-lesional halo, multiple nodular lesions, consolidative/cavitary lesions are also found during some disease stages. About 75% of patients harbor lesions exhibiting peripheral predominance with unilateral lung involvement. More than half of our study population (64%) lost their lives within a month despite aggressive medical and surgical treatment, reflecting the aggressiveness of the disease.

Conclusions: This study concludes that the presence of reverse halo sign (RHS) on lung CT in Covid infected/recovered individuals was found to be a stronger indication of pulmonary mucormycosis. Hence, CT might guide the physicians to start suitable therapy earlier and enhances the outcome.

Keywords:- *Black fungus infection; COVID-19; CT features; Pulmonary Mucormycosis; Reverse halo sign; Zygomycetes.*

I. INTRODUCTION

With the increasing prevalence of Covid associated mucormycosis worldwide, people have entered a new state of panic and chaos. While COVID-19 was already a major concern, the deadly fungal infection associated with it has sparked widespread concern around the globe. The basic explanation that seems to help Mucorales spores for developing in Coronavirus victims is the low oxygen state (hypoxia) and high blood glucose (uncontrolled diabetes mellitus, new-onset hyperglycemia, steroid-induced hyperglycemia), acidic environment (metabolic acidosis, diabetic ketoacidosis [DKA]), elevated iron levels (elevated ferritins), and decreased phagocytic activity of white blood cells (WBC) due to suppressed immunity (sars-cov-2 mediated, corticosteroid-mediated or background comorbidities) coupled with numerous other shared risk factors such as long-term hospitalization (nosocomial contamination) without or with mechanical ventilators [1-4]. The relationship between Covid-19 and Mucormycosis is shown in Table I.

Mucormycosis (the black fungus infection), formerly known as zygomycosis, is an emerging opportunistic fungal infection caused by the Mucorales [5]. It usually affects sinus cavities, eyes, brain, skin, lungs, and gastrointestinal tract [6]. Although rhinocerebral mucormycosis is the most prevalent form of mucormycosis, several cases of lung involvement, or pulmonary mucormycosis, have been reported during the COVID-19 pandemic. Patients with pulmonary mucormycosis often have non-specific symptoms such as mild fever, cough, hemoptysis, shortness of breath, chest pain, facial edema, and orbital/sinus syndrome [7]. In some cases, if the infection progresses and is not treated in time, it may lead to the development of pleural or pericardial effusion. Sometimes even the infection can involve the contralateral lung making the disease difficult to treat. The increased incidence of covid associated mucormycosis cases has been documented in Asian countries, among which India only shows an incidence of 0.14 cases per 1000 people, which is almost 80 times that of developed countries [8].

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While pulmonary mucormycosis (PM) infections are on the rise these days compared to other lung fungal infections including Aspergillus and Candida infections, a prompt and accurate diagnosis is required owing to its aggressive nature, otherwise, it can even take the lives of patients within a couple of months if treatment is delayed. In addition, accurate diagnosis is also essential for effective treatment, sometimes involving the use of more toxic antifungals than those used to treat aspergillosis, as well as more extensive surgical interventions [9]. Pulmonary mucormycosis is difficult to diagnose clinically due to clinical symptoms that coincide with another lung bacterial and fungal infections and the lack of blood markers such as galactomannan and β-d-glucan [10]. As a result, its conclusive diagnosis frequently necessitates intrusive sampling, which might cause treatment to be delayed and is not always successful. Therefore, radiologists can play an important role in such situations by recommending specific imaging clues that can aid in the diagnosis.

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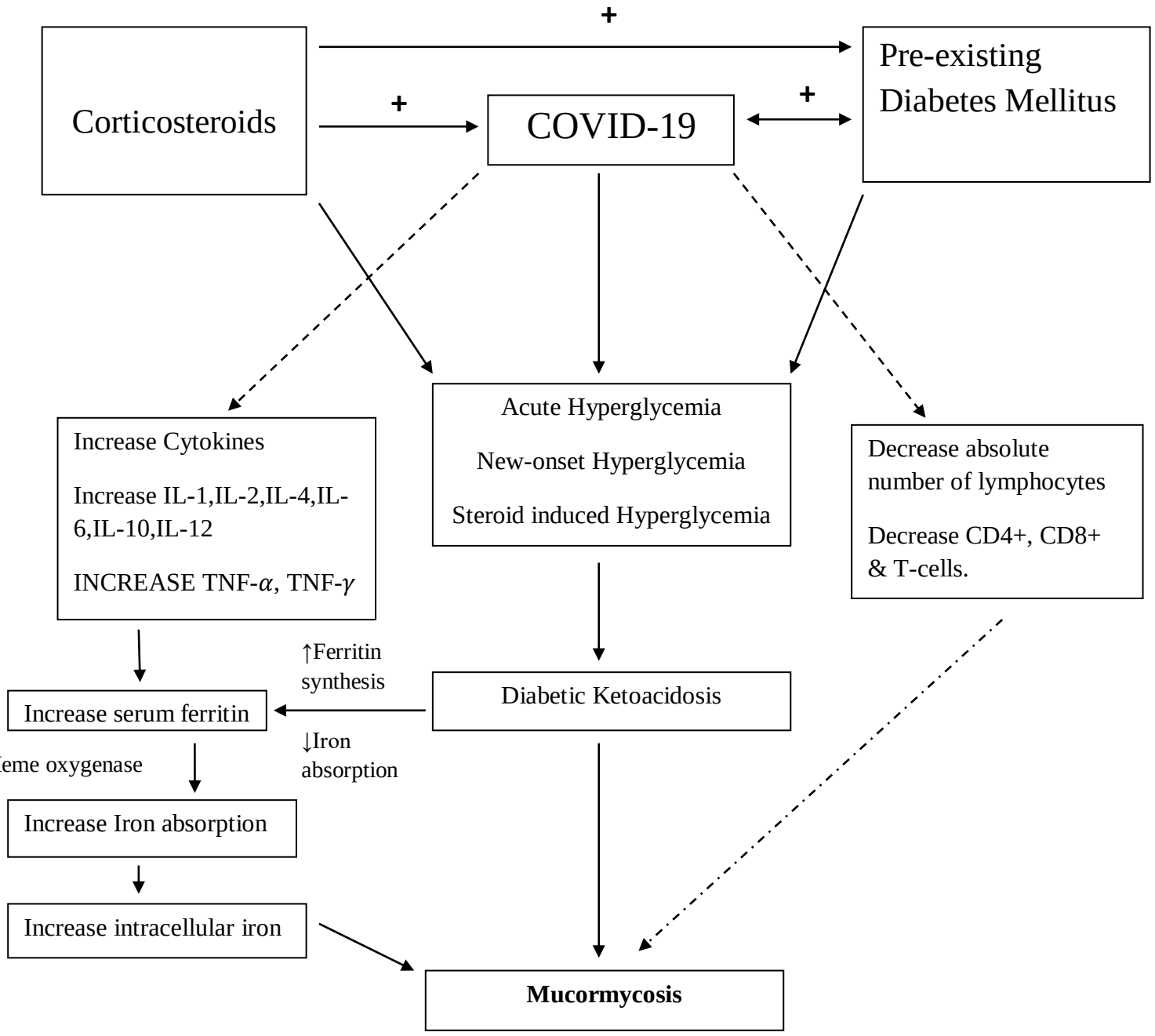

Table 1: Schematic diagram to show the correlation between Covid-19 and Mucormycosis

II. MATERIALS AND METHODS

A. *Patient Selection*

This study grants permission from the institutional review board of our hospital. We reviewed the medical records of all patients of our hospital who were covid-19 positive or just recovered from Covid-19 and histopathologically diagnosed with pulmonary mucormycosis during a period of 6 months (January-June 2021). The institution provided access to patient records and patient confidentiality was maintained. Only 8 patients were found for our study, out of 110 who met our inclusion criteria as this is what to be expected with a rare disease.

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Inclusion criteria were:-

- Active/recovered Covid-19 patients between the age group 32 to 74years were included in our study.
- Cases of pulmonary mucormycosis proven histopathologically in Covid-19 patients with the presence or absence of other risk factors.
- Pulmonary mucormycosis patients who have had at least one CT scan during our study duration.
- Exclusion criteria were:-
- Cases of pulmonary mucormycosis with histopathological confirmation but no history of Covid-19, despite the presence of other risk factors.
- Cases of mucormycosis involving other systems except for lungs.

B. Acquisition of CT images

All CT scans were performed by conventional CT scanners using a Philips machine (Brilliance 6 slice Philips Medical System, Best, Netherlands) and 64-row multi-slice helical CT images were obtained. The slice thickness was 10mm and the scanning was done from just above the sternoclavicular joint to the lung base. The decubitus of all patients was supine position while performing CT scan. Technical parameters were X-ray tube current 100 mA; tube voltage 120 kV; collimation 5 mm; rotation speed 0.5 s; matrix 512 × 512. All image data were interfaced directly to our picture archiving and communication system. Monitors were used to viewing both mediastinal and lung window images.

C. Radiological Evaluation

Two thoracic radiologists who were kept blind regarding the patients' characteristics and clinical outcomes reviewed each patient's CT images to determine the earliest CT features that could be linked to the pulmonary mucormycosis infection and a final judgment was reached after a consensus discussion. These CT images were looked for the following characteristics: GGOs/nodules/masses/consolidations, single/multiple lesions, unilateral/ bilateral lesions, the diameter of the lesion, peripheral/central location of lesions, presence of the reversed halo/bird's nest sign, presence of a large perilesional halo, presence of cavitation, bronchial wall thickening, pleural effusion, and pericardial effusion. Here, GGOs are characterized as ill-defined homogenous hazy grey areas without obscuring the underlying pulmonary vessels, nodules as round or spherical lesions with well-defined margins, and consolidation defined as ill-defined homogeneous radio-opaque areas that obscure the underlying pulmonary vessels. The reverse halo sign (RHS) is known as a central ground-glass opacity lesion encircled by a dense ring of consolidation, regardless of size (Fig. I) [11, 12] whereas, the bird's nest sign (BNS) is known as a mass-like lesion encircled by a ring of consolidations >3 cm in diameter, interspersed with core necrotic low attenuation, tiny cavities, and groundglass opacities (Fig II. A, B)[13]. As both RHS and BNS signs appear to be the same radiologically, some authors prefer to refer to them as the Atoll sign or RHS, which is the preferred nomenclature according to the Fleischner Society [14-16]. The halo sign is defined as a peripheral ring of ground-glass opacity encircling a lung nodule or mass [16, 17]. These signs are usually seen in susceptible individuals who are more prone to invasive fungal infections like angioinvasive Aspergillus infection or mucormycosis [18].

III. RESULTS

During the study period, we only found 8 cases (7 percent of total Covid patients) of pulmonary mucormycosis in people with recovered or active (RT-PCR diagnosis) COVID-19 disease. The participants in our study were 6 (75%) men and 2 (25%) women, ages ranging from 32 to 74 years (median, 60 years) (Table II). The major predisposing factor present in our study group was hyperglycemia. Approximately 88% of the patients in our study had a history of hyperglycemia, and 13% of the patients received a bone marrow transplant due to aplastic anemia.

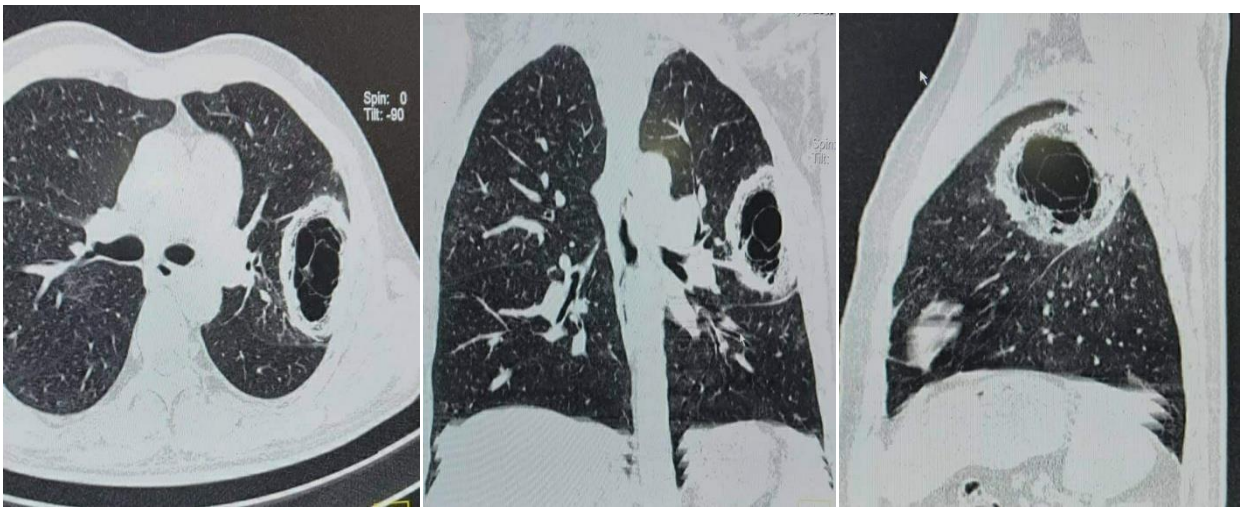

Fig. 1: HRCT demonstrating reversed halo sign in Covid-19 pneumonia patient with pre-existing diabetes mellitus.

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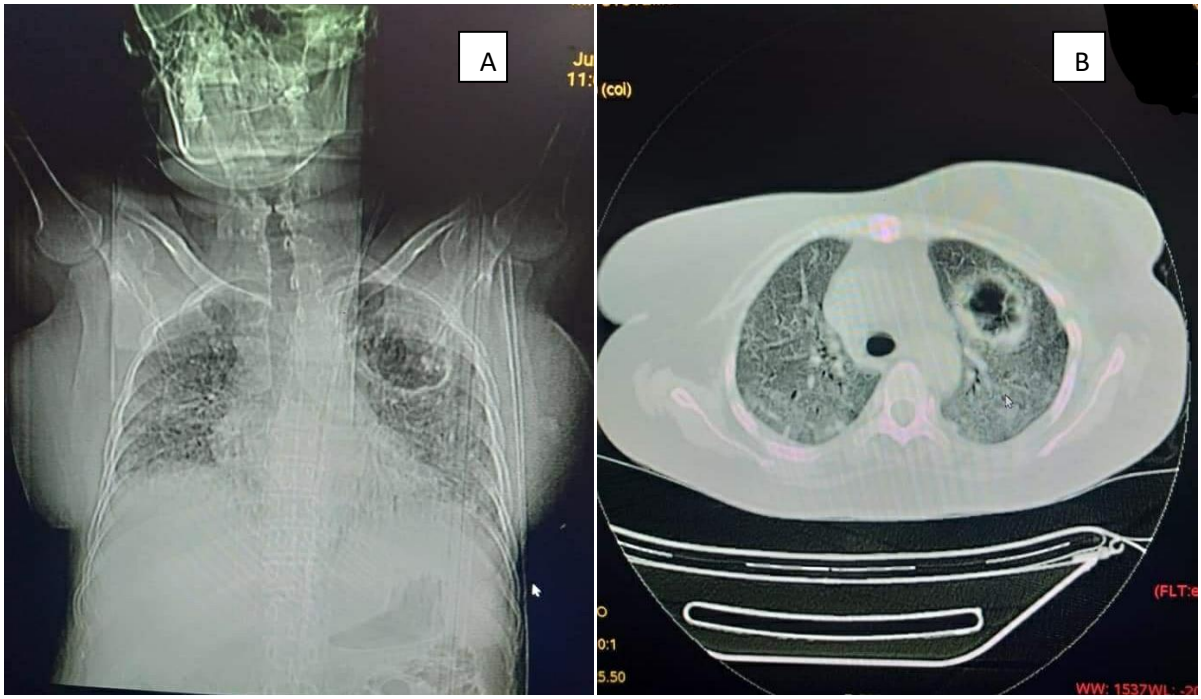

Figure II. A) Chest X-ray PA view of a 42-year-old woman who recovered from Covid-19 last month showing cavitary lesion in the left upper lung lobe. PA, posteroanterior B) Thin-section chest CT scan of the same patient showing a round-shaped cavitary lesion with intervening thin septa and background of GGOs within the cavity i.e. bird nest sign (BNS) in the right upper lung lobe, which is compatible with pulmonary mucormycosis.

Characteristics	No. of patients (%)
Age (in years)	
Range	32 to 74 years
Median	60 years
Gender	
Male	6 patients (75%)
Female	2 patients (25%)
Predisposing factors	
Hyperglycemia Pre-existing DM New onset hyperglycemia or Steroid induced hyperglycemia	7 patients (88%) 3 patients (43%) 4 patients (57%)
Bone marrow transplant (for aplastic anaemia)	1 patient (13%)
Drugs used during management of Covid-19 cases	
Corticosteroids	8 patients (100%)
Remdesivir	4 patients (50%)
Tocilizumab	1 patient (13%)
Clinical Manifestations	
Fever	6 patients (75%)
Chest pain	7 patients (88%)
Cough	4 patients (50%)
Hemoptysis	1 patient (13%)
Opthalmoplegia	1 patient (13%)
Blood Counts	
Neutropenia	7 patients (88%)
Lymphocytosis	1 patient (13%)
Methods used for diagnosis	
Biopsy Transbronchial biopsy CT-guided percutaneous lung biopsy Biopsy refused	7 patients (88%) 4 patients (50%) 3 patients (38%) 1 patient (13%) LAMA
Patient Condition	

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At 14th day,	
Improvement Worsening	2 patients (29%) 5 patients (71%)
At 28th day,	
Recovered Deaths	2 patients (29%) 5 patients (64%)

Table II. Characteristics of pulmonary mucormycosis in Covid-19 confirmed or recovered individuals

Note: LAMA=Leave Against Medical Advice

Among 88% of hyperglycemic patients, only 43% had pre-existing diabetes mellitus, while the remaining 57% had new-onset hyperglycemia or steroid-induced hyperglycemia. In this study, 100% of patients have used corticosteroids for COVID-19 treatment, followed by remdesivir (4 patients, 50%) and tocilizumab (1 patient, 13%).

The clinical manifestations noted in our study group were fever (6 patients, 75%), chest pain (7 patients, 88%), a cough (4 patients, 50%), and hemoptysis (1 patient, 13%). 1 patient (13%) also presented with decreased vision and left eye swelling. i.e. Ophthalmoplegia. According to the available information on total blood count, 88% of patients were having neutropenia and only 13% of patients were having lymphocytosis at the time of diagnosis.

While reviewing the medical records of the patients in our study, we discovered that each of the eight patients had their chest CT scan done at a different time period. To the best of our knowledge, computed tomography (CT) scans were performed for the detection of recurrences or complications of Covid-19, as the country was fighting with it but unfortunately, the features of the fungal lesions were noticed, and CT scan findings were subsequently analyzed.

Around 75% of patients in our study had RHS on their chest CT at their first visit to the hospital, while 13% had ground-glass lesions and the remaining 13% patients had a large peri-lesional halo. Most patients (63%) had multiple lesions, and only 38% of patients had single lesion on their chest CT in our study group (Table III). About 75% of lesions are peripherally situated with unilateral lung involvement. The size of the lesion ranged from 2.1 to 11.9 cm in diameter, with an average of 4.2 cm.

All of these patients had biopsies of the discovered lesion for confirmation of diagnosis, therefore four patients (50%) had transbronchial biopsy, three patients (38%) had CT-guided percutaneous lung biopsy, and one patient (13%) declined any biopsy and left against medical advice. The biopsy specimens were then cultured, and the culture showed the presence of Zygomycetes species in all 7 patients.

On day 14th, 5 patients had follow-up chest CT scans due to worsening of their health status, and several signs were noted that could indicate an increase in the severity of mucormycosis lesions. For example, an increase in the number of lesions was detected in all 5 patients (71%), an increase in the size of lesions was noted in 3 patients (43%) and consolidative changes/cavitary lesions with air bronchogram were noted in 1 patient (14%). The majority of these lesions were found to be perivascular in nature in our study. None of the patients in our study demonstrated pleural or pericardial effusion. In this study, Diagnoses were solely made based on the correlation of CT findings with histopathology of resected or biopsied specimens. Despite aggressive medical and surgical intervention, all 5 patients lost their lives within a month which comprises more than half of our study population (64%) while only 2 patients (29%) remain to survive.

CT Features	No. of Patients (%)
At the time of 1st visit (Total = 8 cases)	
Reverse halo sign	6 cases (75%)
Ground glass lesion	1 case (13%)
Peri-lesional halo	1 case (13%)
No. of lesions per patient	
Single lesions	3 cases (38%)
Less than 3 lesions	4 cases (50%)
More than 3 lesions	1 cases (13%)
Diameter of the largest lesion (cm)	
Median	4.2
Range	2.1 to 11.9
Location of lesion	
Peipheral	6 cases (75%)
Central	2 cases (25%)
Laterality	
Unilateral	6 cases (75%)
Bilateral	2 cases (25%)
Follow-up CT at 14th day (Total = 5 cases)	

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Multiple nodular lesions	4 cases (80%)
Consolidative/cavitary changes with air bronchogram	1 case (20%)
Bronchial wall thickening	1 case (20%)
Pleural effusion	0 case
Pericardial effusion	0 case

Table 3: CT features of pulmonary mucormycosis in Covid-19 confirmed or recovered individuals

IV. DISCUSSION

Mucormycosis cases are not new to us, yet many people die as a result of the disease's early diagnostic difficulties. It's a life-threatening infection caused by Mucorales fungi that are usually associated with a high fatality rate despite medical and surgical therapy. Although it's a rare fungal infection, nowadays its incidence is known to be rising. The rise in mucormycosis incidence is attributable to COVID-19, which is linked to a weakened immune system in infected patients. The impaired immunity of COVID-19 patients is mainly due to injudicious use of steroids, Covid19 induced cytokines, and the presence of other predisposing factors like diabetes mellitus (DM), hematological malignancies, etc. In our study, Pulmonary mucormycosis was seen in 88% of COVID-19 patients with associated hyperglycemia and only 13% of Covid-19 patients with bone marrow transplants. Among total hyperglycemic patients, new-onset hyperglycemia or steroid-induced hyperglycemic patients exceed pre-existing diabetics patients. This may be related to the widespread use of steroids in the treatment of Covid-19. Similarly, DM was also found in 93% of cases of mucormycosis in patients with COVID-19 in a study conducted by John et al [19], while 88% of cases had received corticosteroids. These findings are in accordance with what we observed during our research.

Almost all of the patients in our study group had symptoms of a respiratory tract infection, with the exception of one patient who had ophthalmoplegia. The majority of the patients in this study exhibited chest pain, fever, and cough, which are vague symptoms that can be mistaken for other lung infections. Therefore, diagnosis based on clinical data is a challenge here. The time from the onset of symptoms to the establishment of a confirmed diagnosis i.e. histopathological examination is time-consuming. Thus, CT can help a lot during this period by adding its features for early identification of PM in Covid-19 affected individuals with predisposing variables. We would also like to state that one of our patients had hemoptysis, which might be related to the fungus's angioinvasive nature.

More than 80% of PM patients in our study were neutropenic at the time of initial diagnosis. Legouge et al. also found that 15 out of 16 PM patients were neutropenic in their investigation [20]. Similarly, Jung et al. also found the majority of patients in their study were neutropenic [21]. Therefore, our study reports that neutropenia is a common finding in the majority of patients with early diagnosed PM.

On the basis of past studies, the reversed halo sign (RHS) was evident in the majority of mucormycosis patients with neutropenia in the early disease stages. In our study, RHS was found in 75% of patients during their initial CT scan and unfortunately, we also noticed that those patients were neutropenic. In some of our cases, in addition to RHS, we also found ground glass lesions, multiple nodular lesions, and consolidation/cavity lesions (Fig III). These differences in chest computed tomography lesions may be related to patients admitted to the hospital at different stages of the disease. Vogl et al. found that five out of nine (56%) PM patients had the bird's nest sign (BNS) in a study [13], and they were the first to characterize the BNS in PM patients whose CT scans were slightly different from the typical RHS. Recently, Legouge et al. also conducted a study and reported RHS in 94% of patients with mucormycosis within the first week of the disease [20]. Therefore, radiologists can't neglect the diagnostic performance of the RHS for the early diagnosis of PM.

In a study including 24 patients with PM, Jung et al. discovered that the RHS occurs within 5 days of symptom onset in one-fourth of patients with PM, but within 14 days of symptom onset in 80 percent of patients in their study [21]. Based on Jung et al.'s research, we can say that 75% of patients of our study might have taken medical attention during the early days of the development of their symptoms while the rest may have taken medical attention at a late disease stage. In previous studies [22], the majority of patients had a peripheral distribution of lesions with unilateral location, which appears to be compatible with our findings. In our study, approximately 75% of patients had a peripheral distribution of unilateral lesions.

During Follow-up CT on the 14th day, our study reported multiple nodular or consolidative /cavitary lesions at a site where ground glass focus or RHS could be observed 2 weeks before. The lesions were found to be increased in size and number with the largest one measuring 4.2cm (median) in diameter with unilateral location except for 2 patients. They have bilateral involvement which indicates the rapid spread of PM among Covid active or recovered individuals.

Our study revealed a mortality rate of 64% and a recovery rate of only 29%. The mortality rate is over double the recovery rate, indicating a terrible outlook for PM patients among Covid-19 survivors, reflecting the disease's high lethality despite advances in medical treatment. Hammer et al. also studied 30 patients with pulmonary mucormycosis and found that the mortality rate was as high as 53%, which is similar to our results [22]. These mortality rates reflected the aggressive nature of PM. To our knowledge, this is the first article to report pulmonary mucormycosis cases from our hospital among active/recovered Covid-19 patients.

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There are several limitations to our study. First, it's a retrospective study conducted in a small group of patients, so the results couldn't be assured. Hence, the study must be conducted using a large sample size for the uniform results, which is not possible with a rare disease. Second, our study only included active / recovered Covid patients with proven pulmonary mucormycosis, so we were not able to evaluate the specificity of our findings. However, we are able to illustrate that the reversed halo sign has been shown to be specific for pulmonary mucormycosis, as many previous investigations have indicated [18, 21]. Third, because our study included Covid patients with pathologically proven pulmonary mucormycosis, it's probable that the spectrum of imaging characteristics associated with Covid-19 infection and pulmonary mucormycosis might have been skewed. However, all of these limitations had no effect on the study's major conclusions about CT scans.

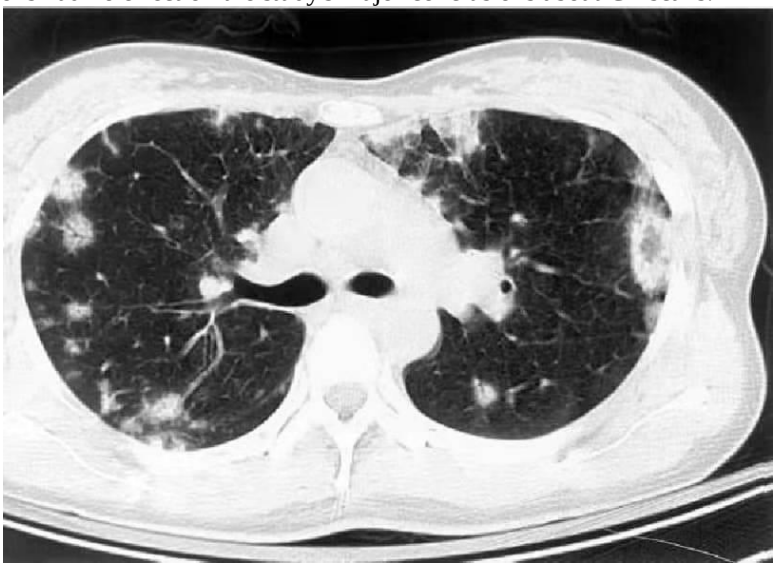

Figure III. A 56-years-old male presented to our hospital with a history of cough and chest pain, after an examination, he was diagnosed with Covid-19 infection (RT-PCR positive). The CT scan of the same patient showing multiple subpleural opacities. The majority of lesions are peripherally situated involving both the lungs. In addition to these, a reversed halo sign can also be seen in the upper lobe of the left lung. Lateron, Biopsy was done and histopathology confirmed it as a case of pulmonary mucormycosis. From the above findings, it is the confirmed case of Covid-19 infection with pulmonary mucormycosis.

V. CONCLUSIONS

Based on our study, the reverse halo sign is more sensitive for pulmonary mucormycosis in Covid-19 positive/recovered patients or immune compromised individuals with neutropenia and it usually indicates the early course of illness. A perivascular ground-glass focus may also be seen along with RHS indicating probable hematogenous dissemination of infection whereas, in severely immunocompromised or terminally ill patients, pulmonary mucormycosis may appear as multifocal pneumonia. During late disease stage, several other lesions like peri-lesional halo, consolidative/ cavitary changes with air bronchogram, bronchial wall thickening, multiple nodular lesions, pleural and pericardial effusion may also be encountered. The Covid affected individuals of the world are more liable to get PM because of uncontrolled diabetes, injudicious use of Corticosteroids, immunosuppressants (tocilizumab and other IL6 inhibitors), and Covid19-induced cytokines. To reduce the risk of deadly mucormycosis, all measures should be taken to maintain optimal hyperglycemia, and corticosteroids should be used with caution in Covid-19 patients. From above, radiologists may be able to suggest a diagnosis of mucormycosis based on the CT findings and the patient's clinical history and clinical symptoms, which could lead to tissue sampling and the administration of suitable medication.

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Conflicts of Interest: The authors declare that there is no conflict of interest regarding the publication of this paper.

Research involving Human Participants and/or Animals: Human Participants. Informed Consent: Written consent had already been taken from the concerned hospital and department for using the patient data to carry out this research.

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