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A Prospective and Retrospective Study of Imaging Characteristics of Acute Invasive Fungal Rhino-Sinusitis (AIFR) on CT Paranasal Sinuses in KOH-Positive COVID-19 Patients

Pranav V K[1], S C Sanjay[2], Vamsi Maddineni[3], Harshavardan[4], Chaitra Srinivas[5]

[1]Assistant Professor, Department of Radiodiagnosis, Kempegowda institute of medical sciences, Bengaluru, Karnataka, India.
[2]Professor and HOD, Department of Radiodiagnosis, Kempegowda institute of medical sciences, Bengaluru, Karnataka, India.
[3]Third year Post graduate, Department of Radiodiagnosis, Kempegowda institute of medical sciences, Bengaluru, Karnataka, India.
[4]Assistant Professor, Department of Radiodiagnosis, Kempegowda institute of medical sciences, Bengaluru, Karnataka, India.
[5]Associate Professor, Department of Radiodiagnosis, Kempegowda institute of medical sciences, Bengaluru, Karnataka, India.

Abstract
Background: Acute (fulminant) invasive fungal rhinosinusitis (AIFR) is distinguished by the invasion of paranasal sinuses and the nasal cavity with fungal organisms. Potassium hydroxide (KOH) helps us to identify the typical pauciseptate/aseptate ribbon-like hyphae and gives us a presumptive diagnosis. The go-to technique for visualising paranasal sinuses is computed tomography (CT). The use of radiological investigations is central to the initial diagnosis and management. We aim to study imaging characteristics of acute invasive fungal rhino-sinusitis (AIFR) on CT paranasal sinuses in KOH-positive COVID-19 patients. **Material and Methods:** The prospective and retrospective study was carried out in the department of Radio-diagnosis at Kempegowda institute of medical sciences, Bengaluru for a period of 8 months on 40 patients. The data was collected from all COVID-19 positive patients with a positive KOH test, subjected to CT of para nasal sinuses. **Results:** Sinonasal mucosal thickening was seen in all subjects. The maxillary sinus was the most commonly affected sinus. Unilaterality and hyperdense contents were observed in about 60% of patients. Peri-antral and pterygopalatine fossa soft tissue infiltration without bone changes indicate neurovascular spread. Osseous erosions, orbital, intracranial and vascular complications were also observed. **Conclusion:** The radiological signs of AIFR in COVID-19 patients vary widely. CT is a valuable tool in diagnosing as well as characterising acute invasive fungal rhino-sinusitis. CT helps determine the extent of the disease which ultimately affects surgical management. Initiation of appropriate treatment is crucial in reducing the high morbidity and mortality associated with acute invasive fungal rhino-sinusitis (AIFR).
Keywords: Acute invasive fungal rhino-sinusitis (AIFR), COVID-19, KOH test.

Corresponding Author: Dr. Pranav V K, Assistant Professor, Department of Radiodiagnosis, Kempegowda institute of medical sciences, Bengaluru, Karnataka, India.

Introduction
In December 2019, an outbreak of pneumonia with an unknown aetiology was first reported in Wuhan, China by a newly emerging coronavirus (severe acute respiratory syndrome coronavirus 2 or SARS-CoV-2).[1] The presence of symptoms, which can range from minor to serious or even life-threatening, may necessitate ICU hospitalisation. The progression of acute respiratory distress syndrome (ARDS) and multi-organ dysfunction are the main causes

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of morbidity and mortality in COVID-19. The most frequently affected patients with invasive fungal infections have pre-existing comorbidities such as uncontrolled diabetes mellitus, AIDS, neutropenia and patients on immunosuppressive or chemotherapeutic drugs.[2-4]

Acute (fulminant) invasive fungal rhinosinusitis (AIFR) is an aggressive fungal infection affecting the paranasal sinuses and nasal cavity that carries a high risk of spreading to the palate, orbital, and intracranial tissues.[5]

Mucor has angioinvasive characteristics that cause it to quickly cross tissue borders and go beyond what is tolerated in an immunocompetent state. This infection spreads primarily via neurovascular bundles, causing widespread tissue necrosis, with high mortality ranging from 50–80%, and high morbidity in patients who survive.[6]

Early and aggressive treatment is essential to successful management. The administration of systemic antifungals is necessary, as is the treatment of underlying comorbidities. Surgical debridement is necessary to remove the necrotic tissue.[7]

Although with reduced sensitivity, microscopy has been the mainstay of diagnosis coupled with culture and histology proof of Mucorales. It is based on isolating and locating the fungus that is causing the ailment. With the use of potassium hydroxide (KOH), we can directly microscopically examine a fresh tissue sample and make a preliminary diagnosis by spotting the distinctive pauciseptate/aseptate ribbon-like hyphae with a sensitivity of 64% and specificity of 90.74%. It is crucial because early therapy with specific antifungal medications can be started to avoid a deadly outcome.

To make the first diagnosis and provide management advice, radiological studies are essential. The go-to technique for visualising the paranasal sinuses is computed tomography (CT). MRI is utilised to assess the orbit, cavernous sinus, perineural dissemination along the trigeminal nerve, and cerebral extension.[8] Imaging results can vary. The diagnosis is suspected when there is severe sinonasal mucosal thickening, evidence of inflammation outside the paranasal sinuses, and characteristics of probable consequences. The diagnosis is not specific to mild sinonasal mucosal thickening.[9]

The use of a systematic approach with a planned checklist is essential for not missing key findings in the radiological report.[5]

We aim to study imaging characteristics of acute invasive fungal rhino-sinusitis (AIFR) on CT paranasal sinuses in COVID-19 patients with a positive KOH test.

Material and Methods

This prospective and retrospective study was conducted in the department of Radio-diagnosis at Kempegowda institute of medical sciences, Bengaluru for a period of 8 months. Based on inclusion and exclusion criteria our study consists of 40 patients.

The data was collected from all symptomatic KOH-positive COVID-19 patients who were subjected to a CT scan of the paranasal sinuses. All COVID-negative patients with previous episodes of adverse reactions to contrast and proven cases of malignancy were excluded from our study.

The institute's ethics committee gave its approval for the project (KIMS/IEC/AO72/M/2021). Prior to the procedure, all patients were informed of it and allowed to give their written consent. To accurately assess the clinical association, a thorough history was obtained. The required surgical treatment (debridement/extirpation) was carried out after a month.

16 slice GE machine was used for the CT study. The frontal sinus roof up to the hard palate was included in the scanning area once the scout projection was obtained. With the patient reclined and the data collecting plane parallel to the hard palate, axial sections were carried out. The pieces were cut at a pitch of 1.4 with slice thickness of 5 mm and a table feed of 7 mm. With a 1 mm overlap, images were rebuilt at intervals of 4 mm. 105 mA, 130 kV, and a 1.5 second tube rotation time were the scanning conditions. Coronal sections were carried out

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on patients who were lying on their backs with their necks extended and in a plane perpendicular to the axial plane. A few patients underwent extended cephalic and caudal sections to observe the disease process' extension. The images resulting from this process were shot at the proper window level and widths to show both soft tissue diseases and bone abnormalities. Brain screening with contrast was done for the required cases to assess intracranial spread. We examined the images for signs of bone degradation, extra-sinus extension, involved sinuses, expanded sinuses, and opacity caused by sick tissue.

RESULTS

All 40 patients were positive for COVID-19 and KOH test. Thirty patients had diabetes, out of which twenty-one patients had uncontrolled diabetes. Seven patients were on immunosuppressant drugs and three patients had HIV infection. The main clinical complaints included headache, nasal discharge, jaw pain, facial and periorbital swelling.

In the present study, nearly 55% of the study subjects were aged more than 50 years of age, 27.5% of subjects were between 41 and 50 years of age and 17.5% were aged less than 40 years. [Table 1]

The majority of study subjects were males (75%) (n=30) and females constituted 25% (n=10) of the study population. [Table 1]

On analysing, maxillary sinus (Table 3) was the most commonly affected sinus among all the four sinuses with 82.5% (n=33) of the subjects followed by ethmoid sinus at 72.5% (n=29) and sphenoid sinus at 50% (n= 20). Frontal sinus was the least affected at 17.5% (n=7) (Figure 2).

Sinonasal mucosal thickening was seen in all the study subjects. A total of 60% (n=24) of the study subjects had hyperdense contents on non-contrast CT. Hyperdense contents on non-enhanced CT are due to the presence of trace elements such as manganese, magnesium and iron salts, elevated protein and decreased water content of secretions. (Image 1)

Air fluid levels (Image 9) were present in 35% (n= 14) of the subjects. Air fluid levels in the sinuses are a diagnostic clue of an ongoing infection. [Table 2]

Soft tissue infiltration of peri-antral fat planes was seen in 67.5% (n=27) of the study subjects [Table 2]. It was noted predominantly along anterior and posterior antral bony walls, outside the sinus perimeter. (Image 6)

Unilaterality was seen in 62.5% (n=25) of subjects, out of which 14 patients had left-side involvement, 11 showed right-side involvement and 15 patients had bilateral involvement of sinuses [Table 2].

72.5% (n=29) of the study subjects showed nasal cavity infiltration (Figure 1). Turbinate hypertrophy (n=18) was the most common finding in nasal cavity infiltration followed by conchal edema (n=11).

Soft tissue thickening causing widening and occlusion of the maxillary ostium (n=19) and obliteration of the osteo-meatal complex (n=14) were noted in our study. (Image 8)

47.5% (n=19) of the study subjects presented with bone erosions [Figure 1]. Osseous erosions were seen involving predominantly the medial walls of the maxillary sinus (n=8), followed by the medial wall of orbit (lamina paprecea) (n=6), nasal septum (n=5) and anteroinferior walls of the sphenoid sinus (n=3). (Image 3)

Bone sclerosis was seen in 25% (n=10) of cases. Bone sclerosis was evident in the sinus walls, hard palate and zygomatic bone giving a mottled appearance. Four patients showed air foci in the bony structures. (Image 10)

Infratemporal and pterygopalatine fossa extension was seen in 30% (n=12) of the patients. Pterygopalatine fossa extension was identified by the presence of soft tissue within the fossa.

Nearly 35% (n=14) of the study subjects presented with orbital extension of the lesion (Figure 6). 9 patients showed orbital cellulitis and fat stranding, 5 patients had thickening and

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enhancement of the medial rectus muscle and 5 patients had proptosis. Right-side involvement was noted in 5 patients and left-side involvement in 6 patients. 3 cases had bilateral involvement of orbits. (Images 4, 5, 8)

Nearly 12.5% (n=5) of the study subjects presented with intracranial extension (Figure 7). The imaging findings in intracranial extension included cavernous sinus thrombosis (n=2), internal carotid artery thrombosis (n=2) and abscess (n=1). (Image 11)

Based on the statistical analysis, various clinical parameters relating to air-fluid levels, soft tissue infiltration, laterality, nasal cavity infiltration, bone erosion, bone sclerosis, pterygopalatine and infratemporal fossa extension, orbital extension, and intracranial extension, with their respective age groups and genders were not statistically significant. This can be attributed to the small sample size of our study. [Tables 4 and 5]

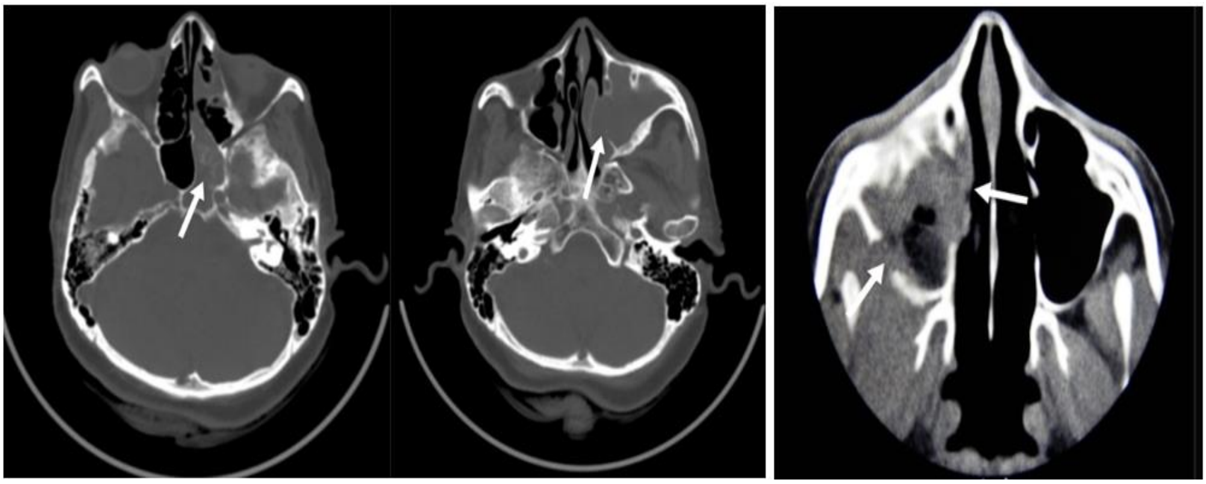

Image 1-3: A) Non contrast CT scan axial section shows obliterative soft tissue density thickening involving the left sphenoid sinus with hyperdense contents within. B) Axial plain CT shows soft tissue thickening in left maxillary sinus with erosions of the medial wall and extension of soft tissue into the nasal cavity. C) Non contrast CT shows soft issue thickening in right maxillary sinus with erosions of medial and lateral walls of maxillary sinus.

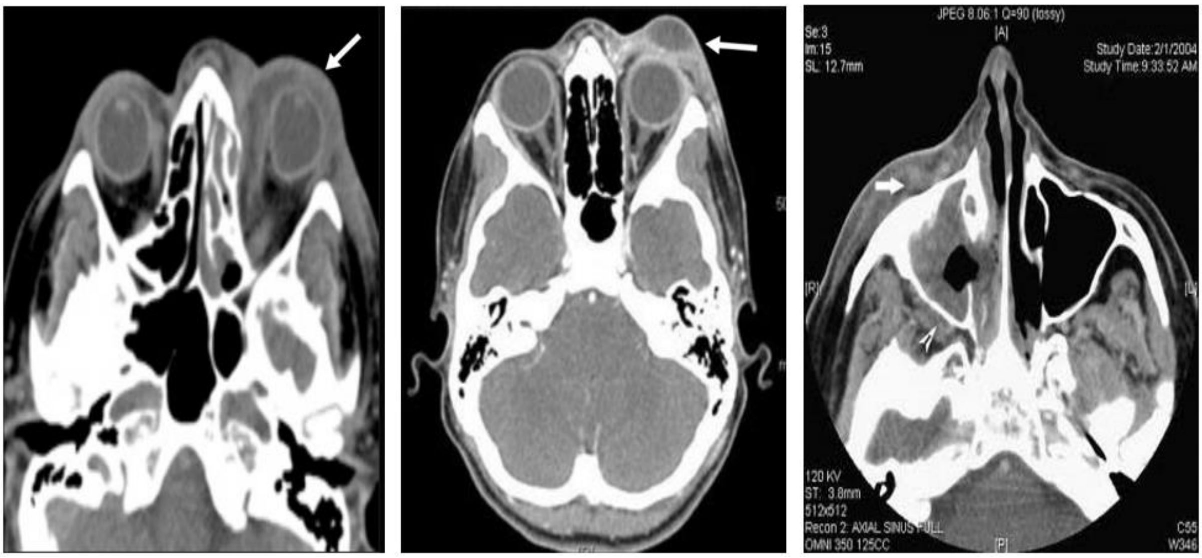

Image 4-6: A) Axial plain CT at the level of orbits show left periorbital cellulitis with mild thickening of medial rectus muscle and soft tissue thickening in left ethmoid sinus. Mild proptosis is also noted. B) Contrast CT scan shows left periorbital cellulitis with a

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rim enhancing abscess C) Axial non contrast CT shows obliteration and thickening of the right anterior and postero-lateral peri-antral soft tissue fat planes.

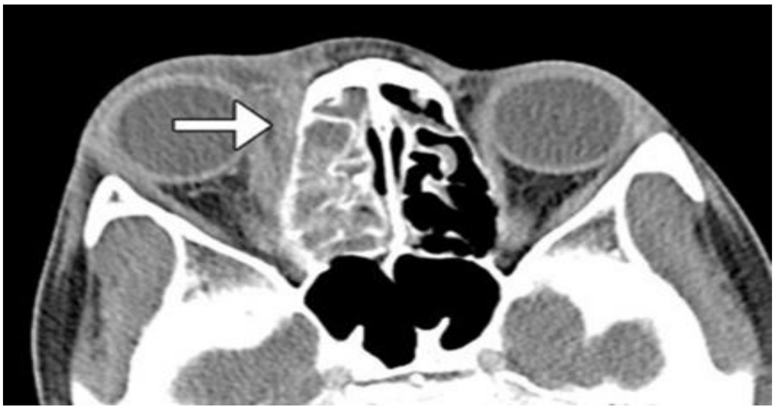

Image 7: Axial Contrast CT scan shows a right subperiosteal phlegmon seen as a soft tissue thickening within the orbital fat adjacent to the medial wall of orbit. Soft tissue thickening is also noted in the right ethmoid sinus.

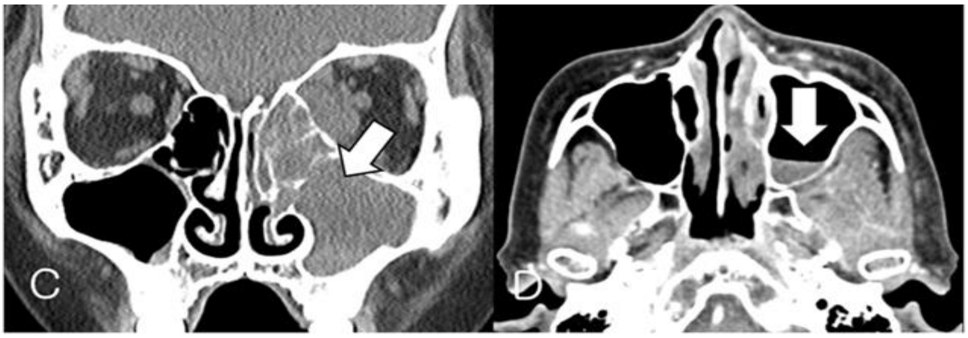

Image 8,9: A) Non contrast coronal CT shows obliterative soft tissue density thickening involving the left maxillary sinus resulting in widening of the maxillary ostium, loss of infundibular air lucency and complete occlusion of the osteo-meatal complex. The soft tissue is seen extending into the left ethmoid sinus. Orbital extension is seen in the form of thickening of the medial rectus muscle. B) Axial plain CT study shows an air-fluid level in the left maxillary sinus.

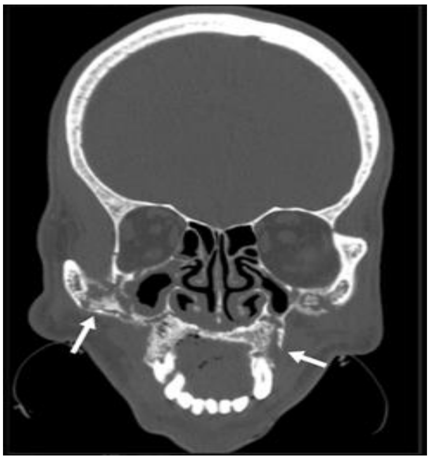

Image 10: Non-contrast CT scan coronal image shows osseous erosions and sclerosis involving the hard palate and bilateral zygomatic bones giving a mottled appearance. Mild soft tissue thickening is noted in the right maxillary sinus with partial occlusion of maxillary ostium.

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Image 11: Contrast enhanced CT image in soft tissue window at the level of skull base shows filling defects in the left cavernous sinus (arrow). Mild periorbital cellulitis and proptosis are seen on the left. There is also sino-nasal mucosal thickening in bilateral posterior ethmoid and left sphenoid sinuses.

Table 1: Distribution of the study subjects based on the age group and gender

		Count	**Column N %**
Age group	Less than 40	7	17.5%
	Between 41 to 50	11	27.5%
	More than 50	22	55.0%
Gender	Female	10	25.0%
	Male	30	75.0%

Table 2: Imaging findings

Imaging findings	**Column N %**
Sino-nasal mucosal thickening	100%
Peri-antral soft tissue infiltration	67.5%
Nasal cavity infiltration	72.5%
Hyperdense contents	60%
Unilaterality	62.5%
Air fluid levels	35%
Bone erosion	47.5%
Bone sclerosis	25%
Orbital extension	35%
Intracranial extension	12.5%

Table 3: Sinus Involvement

Sinus involved	**Column N %**
Maxillary sinus	82.5%
Ethmoid sinus	72.5%
Sphenoid sinus	50%
Frontal sinus	17.5%

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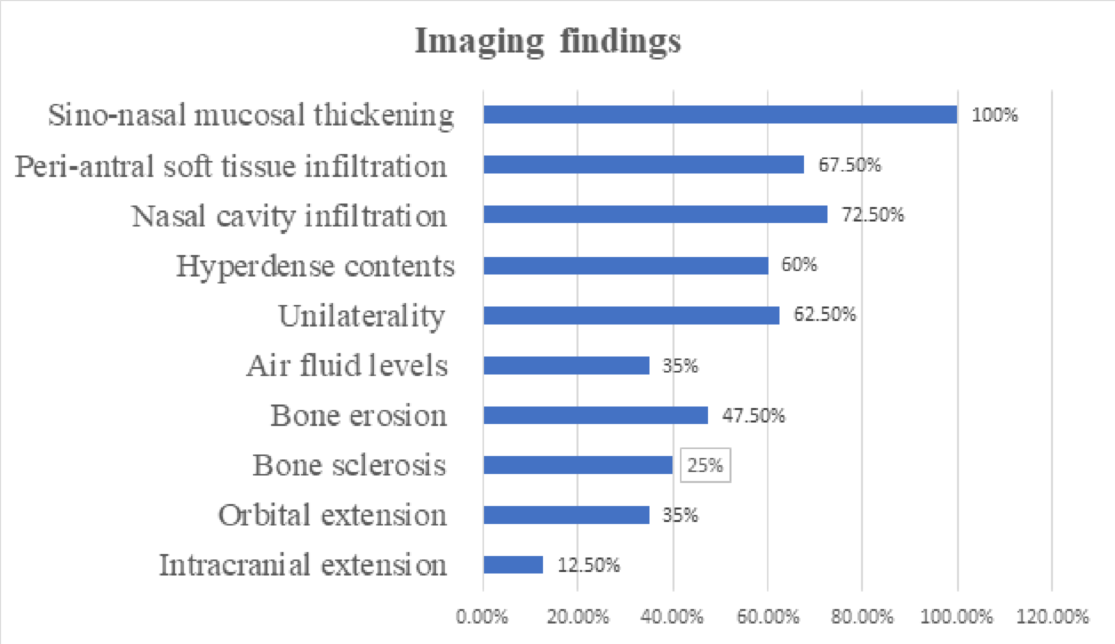

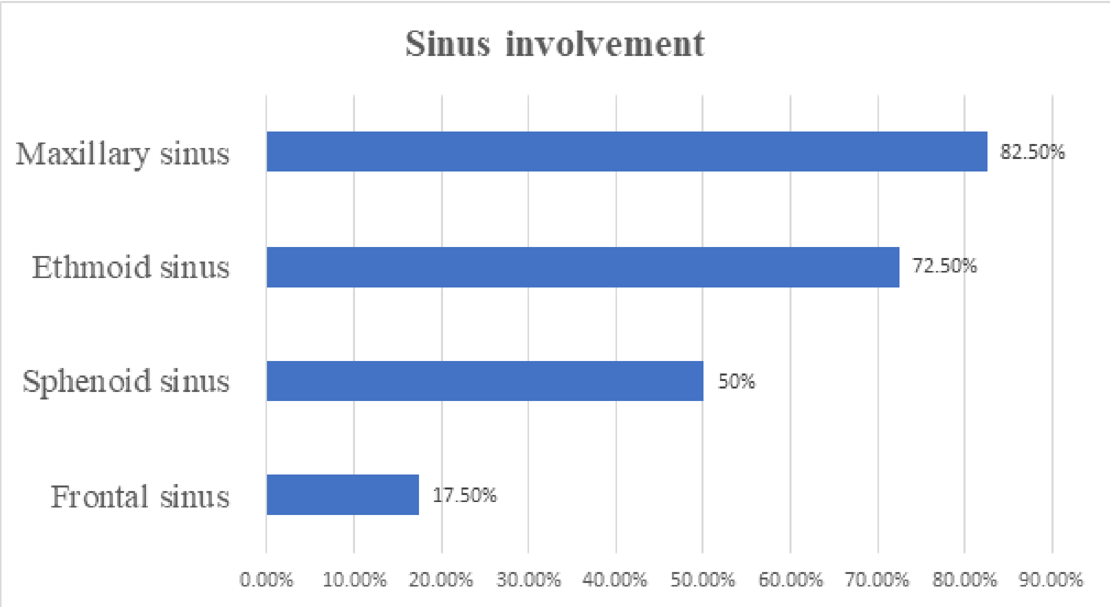

Table 4: Association of age groups and various clinical parameters in the study

		Age group						P Value
		Less than 40		**Between 41 to 50**		**More than 40**		
		Count	**%**	**Count**	**%**	**Count**	**%**	
Air Fluid Levels	Absent	5	71.4%	8	72.7%	13	59.1%	0.686
	Present	2	28.6%	3	27.3%	9	40.9%	
Soft Tissue Infiltration Of Periantral Fat Planes	Absent	2	28.6%	2	18.2%	9	40.9%	0.409
	Present	5	71.4%	9	81.8%	13	59.1%	
Laterality	Bilateral	3	42.9%	4	36.4%	8	36.4%	0.979
	Left	3	42.9%	4	36.4%	9	40.9%	
	Right	1	14.3%	3	27.3%	5	22.7%	

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Nasal Cavity Infiltration	Absent	1	14.3%	5	45.5%	5	22.7%	0.267
	Present	6	85.7%	6	54.5%	17	77.3%	
Bone Erosion	Absent	4	57.1%	5	45.5%	12	54.5%	0.854
	Present	3	42.9%	6	54.5%	10	45.5%	
Orbital Extension	Absent	6	85.7%	5	45.5%	15	68.2%	0.195
	Present	1	14.3%	6	54.5%	7	31.8%	
Intracranial Extension	Absent	7	100.0%	8	72.7%	20	90.9%	0.180
	Present	0	0.0%	3	27.3%	2	9.1%	
Hyperdense contents	Absent	2	28.6%	3	27.3%	11	50%	0.360
	Present	5	71.4%	8	72.7%	11	50%	

Table 5: Association of gender group and various clinical parameters in the study

		SEX				**P Value**
		F		**M**		
		Count	**%**	**Count**	**%**	
Air Fluid Levels	Absent	8	80.0%	18	60.0%	0.251
	Present	2	20.0%	12	40.0%	
Soft Tissue Infiltration Of Periantral Fat Planes	Absent	3	30.0%	10	33.3%	0.845
	Present	7	70.0%	20	66.7%	
Laterality	Bilateral	3	30.0%	12	40.0%	0.292
	Left	6	60.0%	10	33.3%	
	Right	1	10.0%	8	26.7%	
Nasal Cavity Infiltration	Absent	5	50.0%	6	20.0%	0.06
	Present	5	50.0%	24	80.0%	
Bone Erosion	Absent	6	60.0%	15	50.0%	0.583
	Present	4	40.0%	15	50.0%	
Orbital Extension	Absent	7	70.0%	19	63.3%	0.702
	Present	3	30.0%	11	36.7%	
Intracranial Extension	Absent	10	100.0%	25	83.3%	0.168
	Present	0	0.0%	5	16.7%	
Hyperdense contents	Absent	4	40.0%	12	40.0%	1.001
	Present	6	60.0%	18	60.0%	

DISCUSSION

AIFR is a serious, perhaps fatal condition. Patients' imaging features may vary. It ranged from mild sinus mucosal thickening to cerebral extension.

In the current study, roughly 55% of the participants were above the age of 50, 27.5% were between the ages of 41 and 50, and 17.5% were under the age of 40. Males comprised 75% of the study participants, while women comprised 25% of the group.

Similar to our investigation, Ekhlas Shaban et al study from 2022 analysed the clinical and demographic data of the 54 patients who were a part of the study. With a median age of 48.06 ±16.5 years and a male-to-female ratio of 55.6%, the age varied from 12 to 73 years.[10]

In Shintani's study, the median age was 58.0 years, and 55.6% of the population identified as male (55.6% male, 44.4% female).[11]

Eight patients were identified by Manar M. Ashour et al in 2021 as having COVID-19 infection symptoms and needing hospital admission at various stages of their disease. Similar to the few cases of AIFR in COVID-19 patients that have been previously reported, the majority of their patients presented at a late stage of the infection; the symptoms of AIFR

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began 12-35 days after the initial diagnosis of COVID-19, with two of those patients presenting with AIFR after recovering from COVID-19 infection.[12]

Acute and chronic types of invasive fungal rhinosinusitis are distinguished; the chronic versions are either chronic granulomatous invasive rhinosinusitis (CIRI) or chronic invasive rhinosinusitis (CIFS) (CGFS).[5]

Similar to our study, in a study by Surendra Singh Baghel et al, the maxillary sinus was the most often affected sinonasal site in the study followed by the ethmoid sinus. Less frequently, the frontal sinus was involved.[13]

Surendra Singh Baghel et al described a total of 46 cases (37.1%) and 38 cases (30.6%) that affected the pterygopalatine and infratemporal fossae, respectively. 23 (18.54%) patients had intracranial extension, which included three temporal lobe abscesses, five frontal lobe abscesses, two parietal lobe abscesses, nine cavernous sinus thrombosis, three internal carotid artery (ICA) thrombosis, and three cases of fungal cerebritis.

Cavernous sinus thrombosis (n=2), internal carotid artery thrombosis (n=2) and frontal lobe abscesses (n=1) were the intracranial findings in our study. Fungal cerebritis and other complications described by Surendra Singh Baghel et al were not observed in our study.[13]

In a similar study done by Joshi et al maxillary sinus involvement was found in all of their 25 study subjects. Hyper-attenuated sinus contents were noted in 6 of the study patients. Bone erosions were noted in 20 patients involving walls of paranasal sinuses. Nine patients showed cavernous sinus thrombosis.[14]

According to a study done by John M. DelGaudio et al, the most common radiologic feature of invasive fungal sinusitis (IFS) in its early stages, which was corresponding with our data, was significant unilateral nasal mucosal inflammatory process with turbinate hypertrophy.[15]

Peri-antral soft tissue infiltration was identified as an early imaging indicator in a research by C S Silverman et al that should alert clinicians to the likelihood of invasive fungal sinusitis which was correlating with our study.[16]

In a study by T. Khullar et al peri-antral fat obliteration along with stranding or thickening of soft tissues was identified as a subtle sign of early acute invasive fungal sinusitis. When these findings are noted with an intact bone, it is considered an indication of the spread of disease through perivascular channels. Seventeen subjects in our study showed peri antral fat obliteration with intact bone.[17]

Another key imaging sign described by T. Khullar et al to indicate extra-sinus invasion was the presence of soft tissue within the pterygopalatine fossa. The route of spread is via the sphenopalatine foramen along the sphenopalatine artery into the pterygopalatine fossa. Twelve patients in our study showed soft tissue within the pterygopalatine fossa indicating extra sinus infiltration.[17]

T. Khullar et al described orbit as the most common extra sinus involvement. Orbital involvement included intra or extraconal fat stranding, bulky and heterogenous extraocular muscles and abscesses. Nine patients in our study showed cellulitis in addition to fat stranding and five patients showed bulky and heterogenous enhancement of the medial rectus muscle. One patient presented with subperiosteal phlegmon (Image 7) which was seen as a soft tissue thickening within the orbital fat bordering the medial wall of orbit.[17]

According to the research done by Se Jin Cho et al in 2021, nine of the eleven patients had diabetic mellitus or hypertension, and 10 patients were under the age of 60 (mean age, 74.2 years). Both bone degradation and sclerosis could be seen in all 11 patients.[18]

In a study by Middlebrooks E et al bone dehiscence had a sensitivity of 100% for AIFR but a low specificity of 40%. Only 10 (25%) patients in our study showed bone sclerosis. In conclusion, imaging results of bone changes such as erosions and sclerosis were shown predominantly by chronic invasive fungal sinusitis in patients of advanced age who had a chronic course of rhinosinusitis.[19]

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White et al reported that invasive fungal infection was associated with the highest mortality rate among COVID-19 patients.[20]

Patients with COVID-19 infection have decreased CD4+ T and CD8+ T cell counts and increased production of cytokines and cell-mediated immunity. This leads to increased susceptibility to fungal infections. The reasons for the high risk of invasive fungal diseases are steroid usage and chronic respiratory tract infections.[21,22]

Our study corresponds with previous literature implicating severe sinonasal mucosal thickening as a common finding in patients with AIFR on CT. This is significant since the prognosis is often favourable when AIFR is restricted to the nasal cavity. Peri-antral inflammatory changes and pterygopalatine soft tissue infiltration with intact bones should raise suspicion towards neurovascular spread.[17,23]

Unfortunately, despite being one of the common findings in AIFR, unilaterality has a low specificity. So unilaterality is not a reliable indicator to predict AIFR personally.[24]

Our findings demonstrate that CT is a useful screening method for AIFR. However, MRI is required to better assess the soft tissues, intra-orbital and intracranial extensions.

CONCLUSION

Acute invasive fungal rhinosinusitis (AIFR) is life-threatening and a progressive infection affecting the paranasal sinuses and the nasal cavity. The origin and cause of fungal sinusitis in COVID-19 patients is inconclusive. Imaging is essential for assessing paranasal sinuses and extra-sinus complications such as orbital and intracranial extensions. CT is a valuable tool in detecting and characterising acute invasive fungal sinusitis. CT helps determine the extent of the disease which ultimately affects surgical management. The most common findings in our study were sinonasal mucosal thickening, nasal cavity infiltration, unilaterality, peri-antral soft tissue infiltration and hyperdense contents. The most common sinus involved was the maxillary sinus, followed by ethmoid sinus. Soft tissue infiltration of peri-antral fat planes and pterygopalatine fossa without bony changes should raise suspicion towards the early invasion of AIFR and perivascular spread. Radiologists need to keep an eye out for such early subtle imaging findings. Although we cannot postulate a theory for the associated incidence between AIFR and COVID-19 due to the limited sample size, we believe that COVID-19 along with prolonged hospital admission may have contributed to the existing comorbidities that resulted in patients being more susceptible to secondary fungal infections. Early clinical findings are often overlooked, however timely imaging helps in prompt diagnosis. Initiation of appropriate treatment is crucial in reducing the high morbidity and mortality associated with acute invasive fungal rhino-sinusitis (AIFR).

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