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SEPTAL PERFORATION & NOSE THE MOST COMMON PRESENTING SITE IN POST COVID 19 INVASIVE FUNGAL RHINOSINUSITIS: OUR EXPERIENCE

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ABSTRACT

INTRODUCTION: Nasal cavity is a favourable site for the growth of fungus in immunocompromised individuals due to humid conditions. There was a sudden emergence of acute invasive fungal infection cases in the second wave of the COVID-19 in India. In the present epidemic, the aggressive nature of the disease in immunocompromised patients leads to the bony septal involvement resulting in non-iatrogenic perforation. The most common nasal sites involved in IFI post-COVID-19 infection were middle turbinate followed by middle meatus and then septum. Post-COVID-19 infection in hospitalised patients who received oxygenation greatly exceeded those who were on room air and did not require oxygenation. **MATERIALS & METHODS:** The objective of this study was to analyse surgically, the most common nasal sites involved by Invasive fungal infections (IFI) in patients who had history of COVID-19 infection & received either of the steroids, immunosuppressive drugs, oxygen or all the three. 120 patients, admitted in the specialised IFI ward of this hospital with a history of COVID-19 infection, gave their consent for inclusion in the study. Patients with no history of COVID-19 infection were excluded from the study. Moreover, patients who did not receive any of the following; Inj. MPS, Inj. Remdesivir / Inj. Tocilizumab and Oxygen for COVID-19 treatment were excluded from the study. The nasal & extra-nasal sites involved by IFI were analysed & documented intra-operatively by the surgeon. All the intra-operative findings were recorded in real-time and saved on the storage device for feedback. Consequently, all the nasal & extra- nasal sites involved by IFI and amenable to surgery, were surgically debrided. Post-op MRI was done after 6 weeks. Second look DNE / debridement was done once the microbiology, HPE and MRI reports were available. Data from all the 120 patients was analysed and most common nasal sites involved by the disease were established. **CONCLUSION**: To the best of our knowledge, this is the first study to identify nasal septum presenting as perforation plus other nasal sites as the most common nasal site invaded by the IFI in post-COVID-19 patients; which proves that there are multiple nasal sites involved by the fungus in patients who receive oxygen, steroids, immunosuppressive drugs and has one or more underlying co-morbidity.

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INTRODUCTION

Invasive fungal infections (IFI) of the sino-nasal cavity are rare in immunocompetent individuals (Singh, 2019). The cases of IFI in immunocompromised individuals are being reported since a very long time. Moreover, various nasal sites involved in IFI are frequently reported intraoperatively.

Outbreak of Rhino-orbito-cerebral mucormycosis cases in recent Coronavirus disease-19 (COVID-19) pandemic worldwide led to an extensive research to find out the root cause for spurt in IFI cases. Post-COVID-19 patients are most susceptible to acquire fungal infection because of poorly controlled Diabetes Mellitus (DM), overdose of injectable steroids and novel drugs like injection (Inj.) Remdesivir and/or injection Tocilizumab which impair the body's defence mechanism to fight the pathogens (Nambiar, 2021).

Nasal cavity is a favourable site for the growth of fungus in immunocompromised individuals due to humid conditions. Excessive use of non-humidified oxygen for prolonged duration in COVID-19 patients resulted in damage of respiratory nasal mucosa; allowing penetration of organisms causing IFI (Banerjee, 2021). Unsanitised oxygen humidifiers, face masks, ventilators along with the use of low quality industrial oxygen, contaminated oxygen cylinders and delivery systems are cited as responsible for fungal colonization in nose (Nambiar, 2021; Rao, 2021). Overall, the proportion of IFI cases post-COVID-19 infection in hospitalised patients who received oxygenation greatly exceeded those who were on room air and did not require oxygenation (Kubin, 2021). There was a sudden emergence of IFI cases in the second wave of the COVID-19 in India (Singh, 2021). In the present epidemic of IFI, the aggressive nature of the disease in immunocompromised patients lead to the bony septal involvement resulting in non-iatrogenic perforation (Sanghvi, 2021). Adherence of fungus to the endothelial cells of the nasal mucosa allowed angioinvasion and thrombosis which led to tissue necrosis, bone exposure and subsequent perforation (Nambiar, 2021). The nasal endoscopy findings were described as black eschar filling the nasal cavity, mucopurulent secretions and a perforation in the bony posterior septum (Fouad *et al*., 2021). The most common nasal sites involved in IFI post-COVID-19 infection were middle turbinate followed by middle meatus and then septum (Nayak, 2021). However, currently there are no studies who reported the most common nasal sites in IFI post COVID-19 infections, who were immunocompromised and received steroid- Injection Methylprednisolone (Inj.MPS), immunosuppressive drugs like Inj.Remdesivir and/or Tocilizumab, oxygen, and prolonged intensive care admission. This cross sectional study aimed to establish the most common nasal sites involved in IFI patients post-COVID-19 infection by intraoperative assessment. History of COVID-19 infection was established by clinical examination, radiological studies (HRCT chest) and Reverse Transcriptase -Polymerase chain reaction test (RT-PCR test). Surgical debridement was done for all the suspected cases of IFI with nasal endoscope who had a history of COVID-19 infection. The data was collected regarding intraoperative findings and final histopathological confirmation of the disease. A review of the surgeon's observations and operation notes was done to enlist the most common nasal sites involved by the fungus.

MATERIALS AND METHODS

This cross sectional study was conducted in the department of ENT which is a tertiary care referral centre between April 2021 and September 2021. The objective of this study was to analyse surgically, the most common nasal sites involved by IFI in patients who had history of COVID-19 infection & received either of the steroids, immunosuppressive drugs, oxygen or all the three. 120 patients, admitted in the specialised IFI ward of this hospital with a history of COVID-19 infection, gave their consent for inclusion in the study. Patients with no history of COVID-19 infection were excluded from the study. Moreover, patients who did not receive any of the following; Inj. MPS, Inj. Remdesivir / Inj. Tocilizumab and Oxygen for COVID-19 treatment were excluded from the study. In some patients, there were no fungal elements found on KOH mount /culture but were still included in the study because clinical profile, intra-operative findings of the surgeon and final HPR were strong indicators of the IFI. In the outpatient department of ENT, patient's detailed history was taken, and complete clinical examination was done; ENT and Head & Neck, ophthalmic and neurosurgical examination. Deep nasal swab was taken and sent for KOH mount to identify fungal elements if any. Complete haemogram and other routine investigations were done. CT scan of the nose and PNS was done to assess the extent of the disease in the nasal cavity and extra-nasal sites. MRI was done to exclude intra-orbital and / or intracranial involvement. In addition, appropriate referrals were given to manage the underlying comorbid conditions; diabetes mellitus, hypertension, and other conditions. Once the patient was fit for anaesthesia, diagnostic nasal endoscopy (DNE) was done, and biopsy taken which were sent for fungal culture, and histopathology examination (HPE). The nasal & extra-nasal sites involved by IFI were analysed & documented intra-operatively by the surgeon. All the intra-operative findings were recorded in real-time and saved on the storage device for feedback. Consequently, all the nasal & extra- nasal sites involved by IFI and amenable to surgery were surgically debrided with 4 mm, 0 degree rod-lens nasal endoscope in the same sitting. Post-op MRI was done after 6 weeks. Second look DNE / debridement was done once the microbiology, HPE and MRI reports were available. Data from all the 120 patients was analysed and most common nasal sites involved by the disease were established. Once the surgical debridement was done, antifungal medications were started prophylactically; namely Inj. Amphotericin B or Tab Voriconazole / Tablet Posaconazole till the final HPR report was available. Patient was discharged once there was improvement symptom wise and clinically. Follow-up was done monthly. At the time of follow- up, serial MRI and DNE were done to look for residual disease if any. For the sake of understanding and ease of calculation, we categorised nasal sites involved, treatment given and co-morbidities

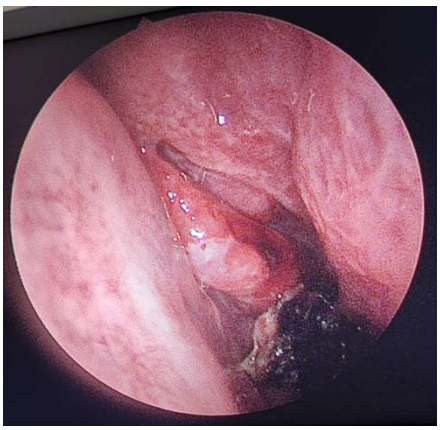

Figure 1: Endoscopic picture showing black turbinate sign

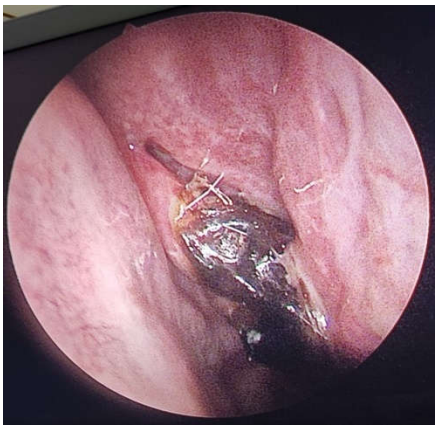

Figure 2: Endoscopic picture showing Black Eschar

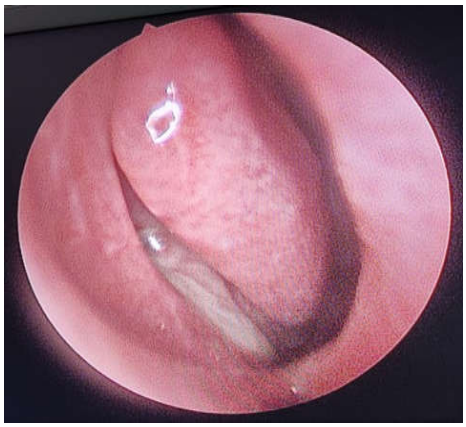

Figure 3: Endoscopic picture showing mucopurulent secretions

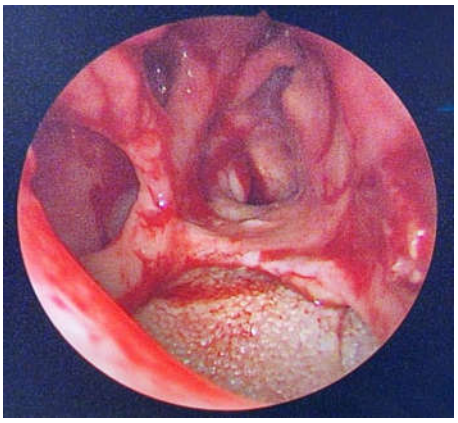

Figure 4: Endoscopic picture showing nasal septal perforation (SP)

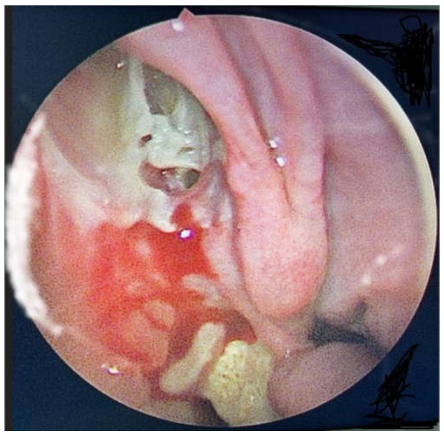

Figure 5: Endoscopic picture showing posterior septal perforation with IFI

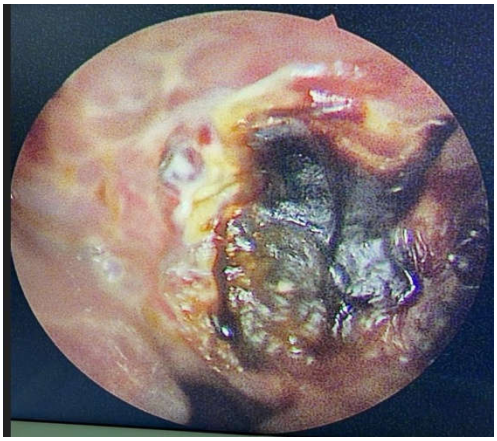

Figure 6: Endoscopic view showing crusting and recurrence of the disease

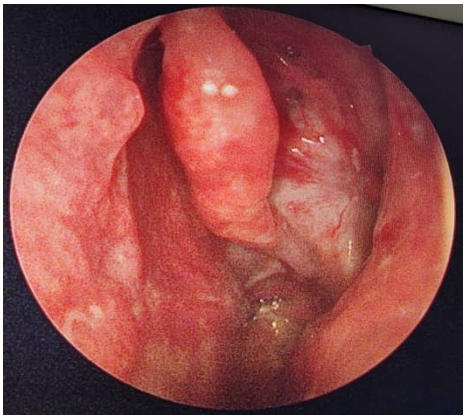

Figure 7: Endoscopic picture showing a well healed nasal cavity

Format for nasal sites

Category 1 Septum – PSP, ASP, SP
Category 2 Septum+ Other nasal sites- PSP +IT+IM+MM, ASP+ IM, SP+ ST
Category 3- MT
Category 4- IT
Category 5- ST
Category 6- Other sites- IT+MT, MM, IM, MT +IM, MT +MM, ST+MM
Category 7- NONE

Format for co-morbidities

Category 1 DM
Category 2 HTN
Category 3 DM+ HTN
Category 4 Other co-morbidities- DM+HTN+post CABG, HTN+ IHD etc
Category 5 None

Format for treatment given

Category 1- Inj MPS+ Inj Remdesivir+ Oxygen
Category 2- Inj MPS+ Oxygen
Category 3- Inj Remdesivir

PSP- Posterior septal perforation HTN- Hypertension
ASP- Anterior septal perforation Inj. MPS- Injection Methylprednisolone
ST- Superior turbinate SP- Septal perforation
MT- Middle turbinate IT- Inferior turbinate
IM- Inferior meatus DM- Diabetes Mellitus
MM- Middle meatus

Statistical analysis:

Results are presented as Mean ± SD and range values for continuous data (Age) And frequencies as numbers & percentages. Categorical data was analysed by Chi-square test. A P value of 0.05 or less was considered for statistical significance. SPSS (Version 18) software was used for data analysis.

RESULTS

120 patients were included in our study with a range of 18-76 years and Mean ± SD of (52.7 ± 10.4).

Table 1. Age distribution

Age (years)	No. of cases	%
< 20	1	0.8
21-40	16	13.3
41-60	77	64.2
61-80	26	21.7
Total	120	100

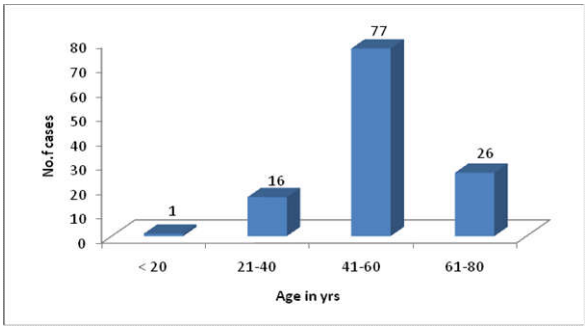

Chart.1. Age distribution

91 were males (75.8%) and 29 were females (24.2%).

Table 2. Sex-wise distribution

Sex	No. of cases	%
Male	91	75.8
Female	29	24.2
Total	120	100.0

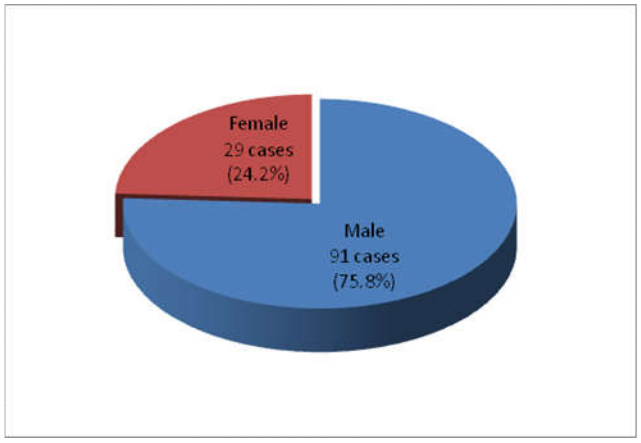

Chart 2: Sex-wise distribution

110 patients (91.7%) were COVID-19 positive; while 10 patients (8.3%) were COVID-19 negative at the time of admission to the IFI ward.

Table 3. Distribution according to Covid status (RT-PCR test result)		
Covid	No. of cases	%
Positive	110	91.7
Negative	10	8.3
Total	120	100.0

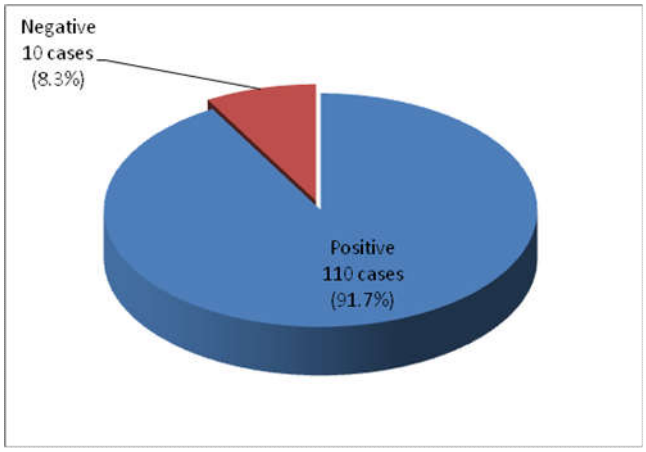

Chart 3. Distribution according to Covid status

Most common comorbid condition was Diabetes mellitus (DM) (n = 63, 52.5%) followed by DM+ HTN (n = 35, 29.2%). 3 patients (2.5%) had Hypertension (HTN). 11 patients (9.2%) had some other co-morbidities. 8 patients (6.7%) did not have any comorbidities.

Table 4: CO-MORBIDITIES		
Co-morbidities	No. of cases	%
DM	63	52.5
HTN	3	2.5
DM +HTN	35	29.2
Others	11	9.2
None	8	6.7
Total	120	100.0

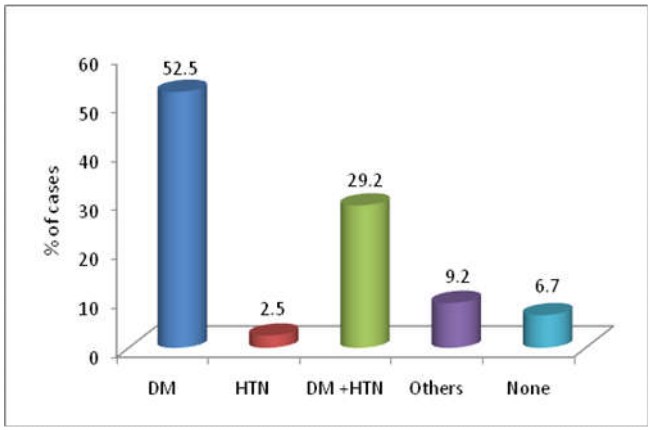

Chart 4: CO-MORBIDITIES

96 patients (80%) received combination of Inj. MPS *plus* Inj. Remdesivir *plus* Oxygen (Treatment Cat 1); 20 patients (16.7%) received combination of Inj. MPS *plus* oxygen (Treatment Cat 2), while 4 patients (3.3%) received only Inj. Remdesivir (Treatment Cat 3).

Table 5: TREATMENT CATEGORIES		
Treatment	No. of cases	%
Cat 1	96	80.0
Cat 2	20	16.7
Cat 3	4	3.3
Total	120	100.0

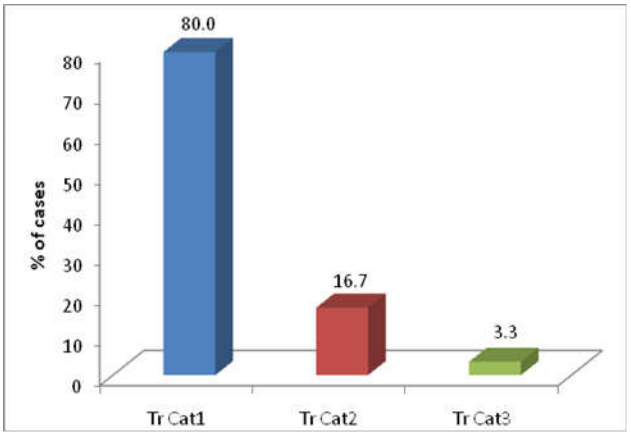

Chart 5: TREATMENT CATEGORIES

Most common nasal site involved by IFI in patients with history of COVID-19 infection was nasal septum (n =78, 65%). 37 patients (30.8%) had only nasal septal perforation [Cat 1]; while 41 patients (34.2%) had septal perforation plus involvement of other nasal sites [Cat 2].

In 42 patients (35%), nasal septum was spared. 42 patients presented with invasion of sites other than the nasal septum. Out of 42 patients, 11 patients (9.2%) had invasion of Middle turbinate (MT) only [Cat 3]. 2 patients (1.7%) had involvement of Inferior turbinate (IT) only [Cat 4]. Superior turbinate (ST) was involved in 3 patients (2.5%) [Cat 5].

Table 6: NASAL SITES		
Nasal site (NS)	No. of cases	%
Cat 1	37	30.8
Cat 2	41	34.2
Cat 3	11	9.2
Cat 4	2	1.7
Cat 5	3	2.5
Cat 6	20	16.7

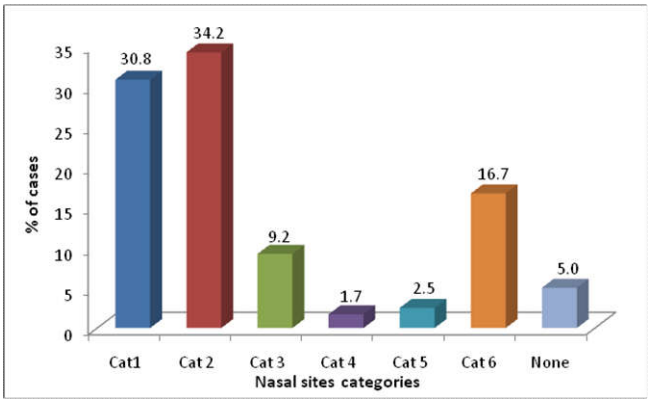

Chart 6: NASAL SITES

Other nasal sites were involved in 20 patients (16.7%) [Cat 6]; while 6 patients (5%) did not have involvement of any nasal sites [Cat 7]. Out of the 120 patients, 108 patients had extension of nasal disease to extra- nasal sites such as maxillary sinus, ethmoid sinus, frontal sinus, sphenoid sinus. Palate and orbit. Palate was seen to be involved in 24 patients, out of which 2 patients had palatal perforation. Out of the 17 patients with orbital invasion, 2 patients underwent orbital decompression. Cases with intracranial involvement and not amenable to ENT surgery were managed by neurosurgeons. In 12 patients there were no extra-nasal sites involved. In 70 patients (58.4%), unidentifiable fungal elements were seen on KOH mount preoperatively. In only 4 patients (3.3%), Rhizopus was confirmed on KOH mount; while in remaining 46 patients (38.3%), no fungal elements were present. Most common organism isolated on HPE was Mucor (n = 87, 72.5%) followed by Aspergillus (n = 21, 17.5%). Aspergillus *plus* Mucor was also seen in some patients (n = 5, 4.2%) while Aspergillus *plus* Rhizopus was found in only 2 cases (1.7%). Candida species was seen in 5 patients (4.2%).

Table 7: KOH MOUNT

KOH mount	No. of cases	%
No growth	46	38.3
Fungal elements +	70	58.4
Rhizopus	4	3.3
Total	120	100

Table 8: Histopathology Report (HPR)

HPR	No. of cases	%
Mucor	87	72.5
Aspergillus	21	17.5
Mucor + Aspergillus	5	4.2
Aspergillus + Rhizopus	2	1.7
Candida	5	4.2
Total	120	100

Out of the 120 patients, 84 patients (70%) were free of the disease after the first Surgery; while 31 patients (25.8%) had the recurrence of disease at the primary Site which were debrided in the second sitting. 5 patients (4.2%) died during the course of medical treatment post-operatively due to intracranial & renal complications.

Table 9: FOLLOW-UP (DNE)

Outcome	No. of cases	%
Expired	5	4.2
Recovered	84	70.0
Recurrence	31	25.8
Total	120	100

DISCUSSION

Mucormycosis of the nasal and extra-nasal sites in the post-COVID infections has been declared as an epidemic in India. The objective of our study was to establish the most common nasal sites involved by IFI in COVID-19 patients

Table 10: Treatment category (Tr Cat) and Nasal site category (Cat) corelation

Nasal site	Tr Cat 1		Tr Cat 2		Tr Cat 3		Total	
	No.	%	No.	%	No.	%	No.	%
Cat 1	33	34.4	4	20.0	0	0.0	37	30.8
Cat 2	35	36.5	6	30.0	0	0.0	41	34.2
Cat 3	11	11.5	0	0.0	0	0.0	11	9.2
Cat 4	1	1.0	1	5.0	0	0.0	2	1.7
Cat 5	1	1.0	1	5.0	1	25.0	3	2.5
Cat 6	15	15.6	4	20.0	1	25.0	20	16.7
Cat 7	0	0.0	4	20.0	2	50.0	6	5.0
Total	96	100.0	20	100.0	4	100.0	120	100.0

$X^2 = 48.16$, $P < 0.001$, Highly Significant.

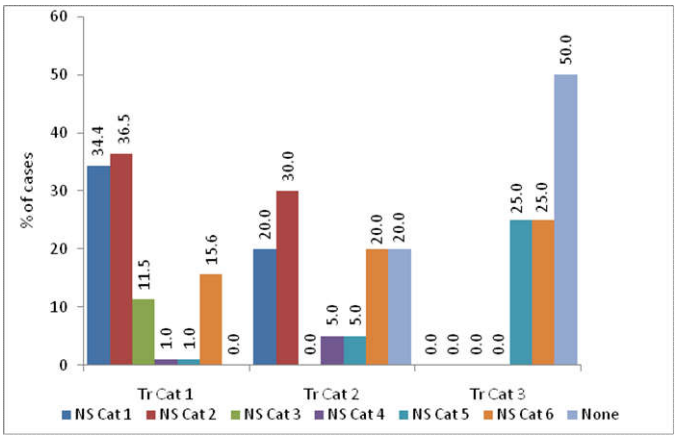

Chart 8. Treatment and Nasal site

who received either of the Inj. MPS, Inj. Remdesivir and Oxygen or all the three. Also, to find if any significant corelation exists between the treatment given for COVID-19 infection and most common nasal sites involved by the fungus post COVID-19 treatment. Indiscriminate use of steroids, drugs like remdesivir and excess use of nasal oxygen facilitated growth of fungus in the nose. In our study, men (n = 91, 75.8%) were seen more frequently to get affected by the IFI than females (n = 29, 24.2%) which was similar to study done by Gupta DP *et al*. In our study, the incidence of IFI was more in middle aged to elderly population. 77 patients (64.2%) were in the age group of 41-60 years; as COVID-19 infection was more prevalent in this age group, which was similar to study done by Gupta DP *et al*.[11] Out of 120 patients, 110 patients were positive by (RT-PCR); while 10 patients were negative at the time of admission to the ward; but were included in the study as they had past history of COVID-19 infection. DM and DM *plus* HTN had a major role to play in our study (n = 98, 81.7%); as in poorly controlled DM, fungal organisms can become pathogenic leading to IFI of the nasal cavity. It is also established that, subset of diabetic COVID-19 patients treated with steroids, oxygen, Remdesivir and/or prolonged intensive care admissions develop rhino-orbito-cerebral mucormycosis.

Table 11: Outcome in relation to Treatment category (Tr Cat)

Outcome	Tr Cat 1		Tr Cat 2		Tr Cat 3		Total	
	No.	%	No.	%	No.	%	No.	%
Recovered	66	68.8	15	75.0	3	75.0	84	70.0
Recurrence	26	27.1	4	20.0	1	25.0	31	25.8
Expired	4	4.2	1	5.0	0	0.0	5	4.2
Total	96	100.0	20	100.0	4	100.0	120	100.0

$X^2 = 0.63$, $P < 0.96$, Non-Significant.

After corelating treatment given and nasal sites involved by the fungus, we found that in patients of treatment Cat 1, the most common nasal site involved intra-operatively was nasal septum *plus* other sites; namely IT, MT, ST, MM and IM; either alone or in combination (n = 35; 36.5%). This corelation was statistically highly significant ($X^2 = 48.16$, $P < 0.001$). In patients, who received treatment Cat 2, the most common nasal site involved was nasal septum *plus* other nasal sites as mentioned above (n = 6, 30%).

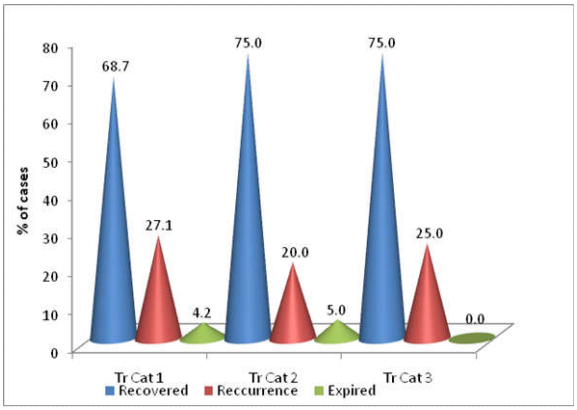

Chart.9: Outcome in relation to Treatment

This corelation was also found to be statistically highly significant ($X^2 = 48.16$, $P < 0.001$). In patients, who received treatment Cat 3, no nasal site was involved (n = 2, 50%). This corelation was also statistically highly significant ($X^2 = 48.16$, $P < 0.001$). From above results it is clear that, nasal septum *plus* other nasal sites was the most common nasal site in patients who received Inj. MPS, Inj. Remdesivir and Oxygen. On the other hand, patients who received only Inj. Remdesivir and did not receive Inj. MPS and Oxygen, showed no nasal site involvement. This proves that combined use of injectable MPS and oxygen along with Inj. Remdesivir have a propensity to involve multiple nasal sites by the fungus. The most common nasal sites involved by the disease, helped us to look for recurrences at the time of follow-up DNE and clear them off the disease if any. In our study, nasal septum invasion was in the form of a perforation. Out of 78 patients presenting with septal perforations, posterior bony septum was involved in 65 patients; while in 6 patients, anterior cartilaginous septum was involved. Whole septal perforation was seen in 7 patients. The most common nasal sites involved by IFI in the immunocompromised patients before the COVID-19 infection era, were middle turbinate followed by middle meatus and then septum but from our study it is clear that the mode of treatment for COVID-19 infection led to an immunocompromised state resulting in IFI of the nasal sites which differed from the sites involved in the pre-COVID-19 era. This atypical presentation of septal perforation was similar to findings seen in study done by Fouad YA *et al* [7] and the single case study done by Al-Khalifa M *et al.*[12] Second most common nasal site was nasal septum only. Third most common nasal sites were Inferior meatus (IM), Middle Meatus (MM) and Superior meatus (SM) either alone or in combination. Amongst the turbinates, middle turbinate (n = 11, 11.5%) was most commonly seen to be affected by the disease which was similar to the study done by Nayak BK *et al*.[3] Extension of the nasal disease to the sinuses, and extra-sinonasal sites such as orbit, palate and brain depicted the aggressive and fulminant course of the IFI in the COVID-19 infections (Sharma, 2021). In clinically or radiologically suspected cases, diagnosis is established by (KOH) wet-mount preparation and HPE of tissue samples obtained from the nasal cavity which demonstrate broad aseptate filamentous fungi branching at right angles with tissue invasion.[10] Many fungal species have been found to cause IFI, but the most commonly identified organisms are Aspergillus and Mucor (Twu, 2021).[13] In our study also, most common HPE report documented was mucormycosis followed by Aspergillus species. In addition, we also found Aspergillus, Rhizopus and candida species in our patients. Role of surgical debridement is to facilitate the use of antifungal medications such as Amphotericin- B which can reach the site of nasal infection and reduce the fungal load & inflammation. After corelating the treatment given category with the outcome, we found that the recovery rate in patients who received Cat 1 treatment was 68.7%. Patients who received Cat 2 treatment, recovery rate was more (75%) while in Cat 3 treatment, it was same as that of Cat 2 (75%). But above corelation was not statistically significant ($X^2 = 0.63$, $P < 0.96$). Recurrence rate was more in patients who received Cat 1 treatment (27%) as compared to Cat 2 (20%) and Cat 3 (25%) patients. But statistically it was not significant ($P < 0.96$).

Similarly, death rate was more in Cat 2 category (5%) as compared to Cat 1 (4.2%) and Cat 3 (0%); but was not statistically significant. From these results, it is clear that treatment given during COVID-19 infection has no significant relation to the overall survival of the patient after surgical debridement and post-surgery medical management for IFI. Hence it is clear that prognosis of the IFI post-COVID-19 infection is dependent on multiple factors and does not depend only on the treatment received before the surgery such as Inj. MPS, Oxygen and Inj. Remdesivir.

CONCLUSION

- To the best of our knowledge, this is the first study to identify nasal septum presenting as perforation plus other nasal sites as the most common nasal site invaded by the IFI in post-COVID-19 patients; which proves that there are multiple nasal sites involved by the fungus in patients who receive oxygen, steroids, immunosuppressive drugs and has one or more underlying co-morbidity.
- Timely intervention in the form of prompt clinical examination, imaging, surgical planning, and medical treatment definitely helps to avoid grave sequelae such as septal perforation, turbinate necrosis, and extra-nasal spread of the disease.
- Avoiding overzealous use of steroids, oxygen and immune-suppressive drugs in COVID-19 patients will reduce the fungal load in the nasal cavity and hence prevent further spread of the disease to the extra-sinonasal sites.

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