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Original Article

A Case Series Discussing Anesthetic Considerations and Statistical Analysis between Rhino-Orbital Mucor-mycosis with Convalescent COVID-19 Status

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Abstract
Introduction: *Rhino Orbital Mucor Mycosis (ROMM) cases were witnessed recently in large numbers. This condition was commonly seen in patients who had recovered from COVID-19 in the previous 3 to 6 months period. The aim to present this case series is to find out ifRhino Orbital Mucor Mycosis (ROMM) in COVID-19 recovered patients are related conditions and whether the pre-existing morbid conditions worsen the clinical picture.*
Methods: *All cases of ROMM for Functional Endoscopic Sinus Surgery (FESS) that presented in our tertiary centre (January to June 21) were sequentially included. Patients (21 to 80 years) of both genders were 99 in number. Patients with uncontrolled systemic condition and COVID positive status were excluded till optimized and/or became COVID negative. Patients underwent optimization of presenting clinical condition from respective departments. Balanced general anaesthesia with endotracheal intubation and controlled ventilation was administered. Patients with diagnosed lower severity of ROMM were extubated on table and those with orbital and neural extension were electively ventilated; also major associated cardiovascular, neurological, renal or respiratory cases were ventilated post-operatively for gradual weaning.*
Results: *Patients were compared in six groups according for oxygen status, oxygen requirement, pre-existing co-morbidities, CT Severity Score, CT Brain findings and intubation difficulty. Oxygen therapy by Non Re-breathing Bag Mask (NRBM) showed P- value 0.029 (statistically significant) and that of intubation difficulty was 0.29 which are statistically not insignificant.*
Conclusion: *The five studied variables are independent and do not contribute to having COVID history as per this analysis.*
Keywords: *Statistical Analysis, Rhino Orbital Mucor Mycosis (ROMM), Convalescent COVID-19 Status*

Introduction

COVID-19 has produced long-lasting effects on immunity. Cellular damage followed by innate immune response with inflammatory cytokine production and pro-coagulant state contribute to post-COVID-19 multi-system sequelae.[1] Permanent damage by fungal invasion of the orbit and brain due to ascending mucormycosis of paranasal sinuses has been witnessed in past few months. Most of the patients were recovered cases of COVID-19 infection which presented with acute onset symptoms, rapidly progressing visual loss and intra-cranial extension of fungus.

Fungal sinusitis either allergic, non-allergic or infective is often an ascending infection affecting the orbit via vascular invasion by fungal hyphae. It is an opportunistic infection often found in immunocompromised patients. [2]

In this series we have attempted to highlight multi-disciplinary management of rhino-orbital mucormycosis (ROMM) in convalescent COVID-19 infection. We have tried to correlate the severity of both with age, preexisting systemic conditions and challenges in treatment.

Materials and Methods

All cases of rhino-orbital mucormycosis (ROMM) operated for FESS (Functional Endoscopic Sinus Surgery), orbital exenterating surgery and nasal endoscopies performed in our tertiary care center were included sequentially.

After obtaining the approval from Institutional Ethics Committee, data about the cases operated as above was compiled for obtaining the relevant answers to the objectives of the study.

Our objective is to analyze association between ROMM and COVID-19 infection history if any. We tried to find whether severity of COVID-19 was impacted by the severity of mucormycosis. We have also studied whether age, intubation difficulty, severity of mucormycosis and preexisting comorbidities are associated factors.

Inclusion Criteria

Diagnosed cases of rhino-orbital mucormycosis (ROMM), Patients of rhino-orbital mucormycosis (ROMM) giving consent for FESS and/or Orbital exenterating surgery and Diagnosed cases of rhino-orbital mucormycosis (ROMM) after optimization of chronic systemic condition were included.

Exclusion Criteria

All patients satisfying inclusion criteria were subjected to anesthesia for FESS surgery for ROMM on emergency basis for life saving purpose. Patients with COVID positive status, febrile patients, patients with history of high grade fever in past 48 hours, hypertensive patients without proper control of BP, poorly controlled DM or those in ketoacidosis and patients with dehydration, loose motions and vomiting were excluded. ENT specific conditions namely acute or chronic sinus related complaints were ruled out. Any history of previous surgery for nasal trauma, polyp or tumors and/or cases with bleeding disorders were not included.

Patients were subjected to thorough pre-operative assessment. Presenting complaints, the duration of complaints, history of presence of previous chronic sinusitis, history of hypertension (HT), ischemic heart disease (IHD), Diabetes mellitus (DM), pre-existing fungal infection or allergic infections was noted. History of having COVID-19 infection and treatment received in recent past of less than six months was noted. History and documentation about hospitalization, ICU admission was also noted.

After history taking, patients were assessed clinically to confirm the information obtained on history. Complete general and systemic examination, followed by airway assessment was done.

All routine investigations, Complete Blood Count, Liver Function Tests, Renal Function Tests and coagulation profile were checked and noted; also specific investigations like x-ray Chest, Blood Sugar profile, CT Thorax, Arterial Blood Gas Analysis if required and Negative COVID-19 report were confirmed.

Depending upon the co-morbidities found, patients were referred to respective specialties for optimization of clinical condition if deranged.

Based on this pre-operative assessment, ASA physical status was ascertained and patients and relatives were explained thoroughly about the existing ailments, proposed surgery and explanation about suspected post-operative incapacitation was verbally explained in mother tongue and written informed consent regarding the risks involved in anesthesia and surgery was obtained.

Patients were subjected to balanced general anesthesia using titrated doses of anti-sialagogues, analgesics, antacids as pre-medication and induction was done followed by muscle relaxation to allow endo-tracheal intubation using cuffed endo-tracheal tube. Maintenance of anesthesia was with Sevoflurane and O_2: N_2O 50:50 concentration. Details about the extent of ROMM were noted and surgical plan was discussed with ENT and Ophthalmic surgeon. After completion of surgery, thorough oropharyngeal suctioning was done to

confirm removal of blood and debris from surgical sites and trachea was extubated after reversal. In cases with diagnosed intracranial extension of ROMM post-operative monitoring and/or elective ventilation was done in ICU.

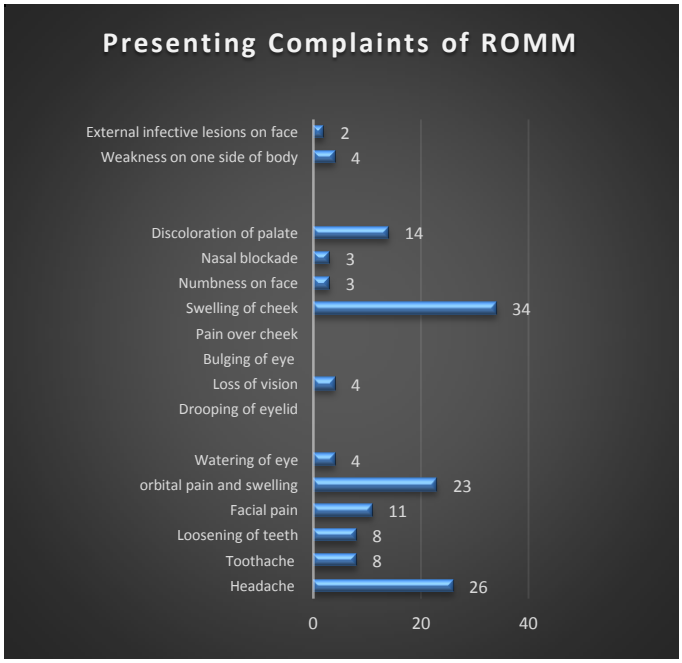
Statistical Analysis

Data was analyzed by using SPSS version 27 (IBM, USA). Quantitative data variables were expressed by using mean and standard deviation. The tests have been performed at confidence interval of 95%. Chi-squared test was used to find the association between requirements of oxygen with age group. Pearson correlation was used to correlate the state of being recovered COVID- 19 patient (dependent variable) with constant predictors like age, CT Severity Score, intubation difficulty and grading of CT brain (independent variables). Further, regression analysis was used to determine if the variability in the dependent variable can be explained by one or more of the independent variables.

Observations and Results

Cases of ROMM operated for FESS surgery (n=99) were included sequentially. Cases operated in our tertiary care institution over January to June 21 were included. Gender wise distribution showed 74 males and 25 females.

Following figure shows presenting complaints of ROMM cases- (Figure 1)



Many patients had more than one complaint depending upon the severity of presentation. Presenting complaints commonly seen were pain and swelling over cheek in 34, headache in 26, orbital pain and swelling in 23, palatal pathology in 14 and facial pain on the same side of disease in 11 patients. Four patients had visual loss when presented, 4 had hemiplegia, 3 had facial numbness and 3 had nasal blockade on the same side of the disease.

Distribution of patients according to age group, Number and Percentage in each group, COVID history in each age group and Details of Oxygen therapy are shown in Table-1.

Chi-square test was used to find the association between requirements of oxygen in various age groups. *P*-value less than 0.05 was considered as significant.

Oxygen therapy by Non Re-breathing Bag Mask (NRBM) shows *P* - value 0.029which is less than 0.05 and hence it is statistically significant.

Oxygen requirements by Nasal Prongs (NP), Face Mask (FM) and BIPAP have *P* - values 0.649, 0.88 and 0.497 respectively indicating that the correlation with age is not statistically significant.

Overall requirement of oxygen showed that 1 patient in age group <30 and15, 21, 17, 10 and 6 patients in the rest of the age groups respectively, required oxygen support. Total 70 out of 99 patients required oxygen; however, *P* = 0.678 shows that there is insignificant association between requirement of oxygen and age group which indicates that oxygen requirement is not impacted by the age of patient. (Table-1)

Table- 1 Distribution of patients according to age group, Number and Percentage and Details of Oxygen therapy

Age in years	Number (%)	COVID n (%)	OXYGEN THERAPY								Total O2 required	
			Nasal Prongs		Face Mask		NRBM		BIPAP			
			Yes	No	Yes	No	Yes	No	Yes	No	Yes	No
<30	2 (2)	2	0	2	1	1	0	2	0	2	1	1
31-40	20 (20.2)	18	6	14	5	15	0	20	3	17	15	5
41-50	31 (31.3)	28	12	19	7	24	2	29	2	29	21	10
51-60	27 (27.3)	22	6	21	8	19	2	25	1	26	17	10
61-70	12 (12.1)	12	3	9	4	8	4	8	0	12	10	2
71-80	07 (7.1)	07	3	4	3	4	0	7	1	6	6	1
Total	**99 (100)**	**89 (89.9)**	***P* -value 0.649**		***P* -value 0.88**		***P* -value 0.029**		***P* -value 0.497**		**Total 70 needed Oxygen. *P*-value 0.678**	

Evaluation of oxygen status of ROMM cases is shown in table 2. Out of total 99 patients, SpO_2on room air could be obtained in 97 and six minute walk test could be performed by 84 patients. Mean values of SpO_2on room air and after six minute walk test were tested using ANOVA for quantitative data variables. The obtained *P* -values, 0.187 and 0.508 respectively, were found statistically insignificant. This shows that there was no statistically significant correlation between severity of COVID history and present oxygen status of ROMM cases. (Table-2)

Table- 2- Evaluation of oxygen status of ROMM cases

Age (years)	SpO_2on Room air		Six minute walk test	
	N	Mean	N	Mean
21-30	2	95.50	1	98.00
31-40	19	97.05	18	95.50
41-50	31	97.23	28	96.32
51-60	27	96.70	22	95.32
61-70	11	95.73	10	94.70
71-80	7	97.00	5	95.20
Total	97	96.82	84	95.64
	P value was 0.187		*P* value was 0.508	

Status of co-morbidity of ROMM cases was studied to find any association of co-existing conditions. Many patients had more than one conditions together. P-value of diabetes, previous, recent and none showed no statistically significant association. (Table-3)

Out of total 99 cases showed presence of recent diabetes in only 32 patients. 40.40% had hypertension and 10.10% had associated ischemic heart disease. Total co-morbidity count was 149. (Table-3)

Table -3 Status of associated co-morbidities ROMM cases

Age in years	Diabetes Mellitus (DM)			Hypertension Number (%)	IHD Number (%)	Total
	No DM	Previous DM	Recent DM			
21-30	0	0	2	0	0	2
31-40	6	9	5	5(5.05)	1(1.01)	26
41-50	5	15	11	7(7.07)	2(2.02)	40
51-60	4	15	8	16(16.16)	5(5.05)	48
61-70	0	8	4	8(8.08)	1(1.01)	21
71-80	1	4	2	4(4.04)	1(1.01)	12
Total	16	51	32	40(40.40)	10(10.10)	149
	P value was 0.452					

Table -4 Status of vital parameters and intubation criteria in ROMM cases

Age (years)	Pulse rate		Mean Arterial Pressure MAP		Mallampati Grade				Intubation difficulty			
	N	Mean	N	Mean	1	2	3	4	0	1	2	3
21-30	2	102.50	2	98.67	0	0	0	2	0	0	1	1
31-40	20	84.10	20	92.63	0	13	4	3	0	11	7	1
41-50	31	96.74	31	94.16	1	10	11	9	2	15	9	4
51-60	27	91.89	27	96.40	1	9	8	8	1	14	10	2
61-70	12	94.17	12	96.36	0	4	5	3	1	6	3	2
71-80	7	92.57	7	95.14	0	2	5	0	0	7	0	0
Total	99	92.37	99	94.89	2	38	33	25	4	53	30	10
Total	*P* value= 0.105		*P* value= 0.842		*P* value= 0.21				*P* value= 0.48			

To find out association of variations in pulse rate and MAP during difficult intubation, Mallampati grades and actual difficulty during intubation were correlated. No significant statistical correlation was seen as the obtained *P* values as mentioned in table-4 show no statistical significance.

Out of 99 total cases, 25 were grade 4 anticipated difficult; actual grade 3 intubation difficulty was experienced in 10 patients. (Table-4)

In table 5 numbers of patients with increasing grades of severity of disease involvement on CT scan are mentioned as grades- 1, 1 & 2, 1, 2 &3, 1, 2, 3 & 4 and 1, 2, 3, 4 &5.

The age-wise distribution of these patients has been shown as number of patients in each grade of severity. The obtained *P* -value 0.113 shows that there is no statistically significant correlation between severities of ROMM with age.

Total 25 patients had grade 5 ROMM, 36 had grade 4 and 24 had grade 3 severe ROMM. From the table it is seen that majority patients with more severe disease fall in 41 to 50 and 51 to 60 age groups.

Table- 5- Special Investigations in ROMM cases

Age (years)	**CT- PNS, Brain and Orbit Severity score 1- Bone involvement 2- Inflammation of sinuses 3- Brain tissue involvement 4- Orbital extension 5- Vascular details, aneurysm or clot**					
	Number of patients with Severity grades					
	1	**1,2**	**1,2,3**	**1,2,3,4**	**1,2,3,4,5**	**Total**
21-30	0	0	0	0	2	2
31-40	0	1	6	9	4	20
41-50	0	7	9	11	4	31
51-60	1	1	5	12	8	27
61-70	0	1	3	4	4	12
71-80	1	2	1	0	3	7
Total	2	12	24	36	25	99
P - value= 0.113						

Regression Analysis

Regression analysis has been established between COVID result as the dependent variable and the following as the independent variables:

Quantitative factors:

- Age
- CT Severity Score (CTSS) (25 being maximum)
- CT Brain (5 being maximum)
- Intubation difficulty (3 being maximum)

Qualitative factors:

- R/P : numerical values assigned as R=0 and P =1
- Existence of co-morbidity : numerical values assigned as YES =1 and NO=0

Annexure Table 1

Model Summary				
Model	R	R Square	Adjusted R Square	Std. Error of the Estimate
1	0.523	0.274	0.227	0.26635

The R^2 is 0.274 which means that 27% of the variance in the dependant variable is explained by this equation.

ANOVA test is used to check the statistical significance of the result. It shows that the null hypothesis that the multiple R is equal to zero is rejected at *P* =.001. This means that R is significant, however, that the results show that the R squared is low indicating that only 27% of the total variance in COVID is explained by these independent factors.

Annexure Table 2

ANOVA						
Model		Sum of Squares	Df	Mean Square	F	Sig.
	Regression	2.463	6	0.411	5.788	<0.001
	Residual	6.526	92	0.071		
	Total	8.990	98			

Annexure Table 3

Coefficients						
Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig. (*P* value)
		B	Std. Error	Beta		
1	(Constant)	1.529	0.168		9.125	<0.001
	Age	0.000	0.002	0.015	0.164	0.870
	CTSS	0.025	0.004	0.503	5.516	<0.001
	R_P	-0.027	0.055	-0.045	-0.491	0.625
	Co-morbidity	0.054	0.061	0.080	0.892	0.375
	CT Brain	0.012	0.025	0.043	0.478	0.634
	Intubation difficulty	0.038	0.036	0.095	1.064	0.290

The test has been performed at 95% confidence interval. At this confidence interval, for a factor to be considered significant, its *P* -value should be lower than 0.05. Hence, the above results show that CT Severity is the most significant contributor to being COVID positive and none of the other factors qualify as significant at this confidence interval.

However, intubation difficulty also has a *P* -value of 0.29 which is quite lower than the others, hence, that too could be considered as a contributor, however not significant as per this analysis.

The p-values of the others shows that they do not contribute to being related to COVID.

Thus, it can be said that as per the combined interpretation of R-squared and the coefficients, these independent factors do not adequately explain the variance in the dependent factor. Only CT Severity Score followed by intubation difficulty have some contribution to having COVID positive history.

Discussion

These COVID-19 recovered patients with dreadful rhino-orbital mucormycosis (ROMM) essentially required proper pre-admission planning, pre-operative evaluation and optimization.

Enhanced Recovery after Surgery (ERAS) a protocol based concept is followed to hasten recovery and involves team efforts between surgeons and anesthesiologists for its active implementation.[3]

Fungal Sinusitis is a known chronic condition involving the nasal cavities and paranasal sinuses. Fungi do not contain chlorophyll hence they obtain nutrients from dead and decaying matter to manufacture their own food. In conditions like Diabetes mellitus, antibiotic overuse, congenital immune disorders, lymphoma and leukemia, where the normal immune mechanism of human body is compromised, fungal conditions prevail. [4]

Out of total 99 cases in this series, 89 (89.9%) patients were recovered COVID-19 patients; 51 were known diabetics and 32 had recent onset diabetes. (Table-3).

Common clinical symptoms of sinusitis are nasal congestion, facial pain, pressure, anosmia, and when immunity is compromised, overlying skin changes with numbness and swelling over face, cheeks and eyes. About 90% cases of sinusitis have been reported to be fungal in origin.[5]

In this series, out of total 99 patients 34 (24%) presented with swelling over cheek, headache in 26 (18%), orbital pain and swelling in 23 (16%), palatal pathology in 14 (10%) and facial pain on the same side of disease in 11 (8%) patients. (Figure 1)

The occurrence of mucormycosis is rare in general population and the previously cited incidence is 0.005 to 1.7 per million.[6] In India, it was reported to be 0.14 per 1000 diabetic patients which is eighty times higher than that reported in rest of the world.[7]

Huang C. et al studied long term consequences of post-COVID-19 patients at six months from onset of symptoms. Out of 1733 patients studied 76% had at least one symptom. Fatigue, muscular weakness was reported by 63%, sleep difficulties by 26% and anxiety depression by 23%. Reduction in health related quality of life-score was positively associated with severity and women were found more prone to have the above symptoms. The prevalence of post-COVID-19 sequelae includes long-term pulmonary effects causing persistent diffusion defects in those who suffered severe COVID disease.[8,] [9]Arnold et al recruited 163 COVID-19 patients, out of which 19 died, 13 were in-patients, and 131 were invited for follow up. Although most patients were improving, 74% reported one on-going symptom, 39% breathlessness, 39% fatigue and 24% insomnia. Of the total patients studied by Arnold et al, 14% showed abnormalities on radiography; two had radiographically worsened interstitial lung disease which had existed previously. High resolution HRCT showed normal features in four, minor persistent ground glass opacities in two, and pleural effusion in one patient. Authors report the limitation of this study as a single centered study and in-patients and patients residing in the nursing homes were not followed. They have inferred that persistent symptoms were present for 8-12 weeks even in patients with mild disease.[9]

To the findings in this series, Pearson correlation co-efficient was applied. Ratio between the co-variance of dependent variable namely age, CT Brain, CT severity score, intubation difficulty and occurrence of associated co-morbidities with COVID history was obtained and the products of their standard deviation was subjected to regression analysis. The linear correlation of this covariance was low (27%). This shows that these variable are independent of each other.

However, according to the table of co-efficient, the *P* value of CT severity score was found less than 0.001, which is highly significant statistically. Thus,

severity of ROMM cases correlated with that of CT Severity because it was the most significant contributor that qualified at the confidence interval of 95%.

Carfi A et al have defined Euro QoL-VAS score (Euro-Quality of Life), as 0-Worst Imaginable Health to 100- Best Imaginable Health to compare the quality of health before and after COVID-19.[10]

Considering that the cells of respiratory tract that are already infected with SARS-CoV-2, secondary infections with ubiquitous environmental molds have been epidemiologically evaluated by Arun Patel et al. Factors like indiscriminate use of antibiotics, inappropriate high dose glucocorticoids and lapses in infection control practices have been attributed to be the root cause of this black fungus epidemic.[11]

Prior to association with COVID-19 the overall mortality rate of mucormycosis was 54%, that due to disseminated mucormycosis was 96% and it was 14.9% associated with diabetic ketoacidosis (DKA). If the immune system is properly functioning, this environmental mold which humans are breathing in regularly, does not cause any disease, however, immune cell dysregulation caused by diabetes inhibits neutrophil chemotaxis and intra-cellular killing of fungal spores. Similarly, excess hyperglycemia in DKA, low pH due to excess acid production in blood and neutropenia due to excessive phagocytic function impairs phagocytosis and makes the tissue vulnerable to fungal infections.[12]

In response to invasion by SARS-CoV-2 pathogen, the cells of the immune system generate significant amount of pro-inflammatory infiltrates, the cytokine storm to halt the viral spread. These infiltrates directly damage the airway epithelial cells leading to respiratory distress and high susceptibility to fungal invasion. [13] During massive COVID-19 outbreak, corticosteroids were prescribed in large quantities and for long durations, thus leaving patients with or without diabetes more susceptible to fungal invasion. We did not have the exact data about steroid therapy in our cases. The limitation was that patients were referred from distant areas and though history of hospitalization was elicited their treatment details could not be obtained.

Choice of anti-fungal therapy is also limited as they are equally toxic to human cells. Karl V. Clemons et al [14] compared the efficacies of anti-fungal amphotericin-B in three different preparations. In their pursuit to identify a safe and effective anti-fungal therapy, they studied mice as experimental animals. They observed that 90% of the control group mice succumbed between 15-34 days post-infection. All mice that received 5-10mg/kg of colloidal dispersion amphotericin-B or Am Bisome, the true lamellar liposome, survived through 49 days of the experiment. Infection from the brain was however found difficult to clear though renal toxicity could be controlled. Toxicity also included production of pro-inflammatory infiltrates again requiring the use of corticosteroids. Hypokalemia and hyperglycemia precipitates in therapeutic doses.

Conclusion

Thus, post-COVID-19 ROMM continues to be a perpetually growing threat to our health. Thorough screening and research of underlying medical conditions is still going on.

From this study we infer that post-COVID-19 ROMM has correlation with CT Severity Score. The five studied variables namely age, CT Brain, CT Severity Score, Co-morbidity and intubation difficulty are independent and do not contribute to having COVID history as per this analysis.

We could not find any significant correlation of CT Severity with pre-existing co-morbidities in COVID-19 recovered Mucormycosis patients.

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