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CEREBROVASCULAR INVOLVEMENT IN PATIENTS WITH COVID-19 ASSOCIATED MUCORMYCOSIS IN TERTIARY CARE CENTRE

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Abstract

Background

This study scrutinizes the prevalence and demographic determinants of rhino-orbito-cerebral mucormycosis (ROCM) in the context of various factors including age, gender, and diabetic conditions, delineating clear patterns and potential risk factors that may contribute to the onset and exacerbation of ROCM.

Methods

This cross-sectional study was conducted to investigate the cerebrovascular involvements in patients diagnosed with COVID-19 associated mucormycosis (CAM) at hospitals affiliated with BMCRI. The study spanned from May 2021 to August 2021, during which time pertinent data from 49 patients were meticulously recorded and analyzed.

Results

The results underscored a significant gender disparity in ROCM prevalence, with males being more predominantly affected ($p < 0.05$)[13]. Furthermore, the age group of 50-60 showed a heightened vulnerability to ROCM, especially amongst individuals with pre-existing diabetic conditions ($p < 0.001$)[15,17,19]. Noteworthy was the exacerbation of symptoms and complications in patients with a history of steroid usage ($p < 0.01$)[20]. A considerable portion of the cases also delineated a discernible difference in clinical outcomes between

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Mucor and Aspergillus infections in ROCM, paving the path for focused clinical strategies[21].

Conclusion

The study furnishes critical insights into the demographic precursors of ROCM, spotlighting age and diabetic conditions as potent risk factors. The findings beckon an immediate need to tailor medical interventions and community health programs that address these specific demographics, thereby potentially curtailing the incidence and severity of ROCM. Further research is advocated to establish a more intricate understanding of the disease dynamics.

Keywords

Rhino-orbito-cerebral mucormycosis, gender disparity, age determinant, diabetes, steroid usage, secondary infections, clinical outcomes.

INTRODUCTION

In recent times, the medical community has been channeling its efforts to understand and address the multi-faceted repercussions of the COVID-19 pandemic, which has unequivocally altered the global health landscape. As clinicians and researchers grapple with the nuances of SARS-CoV-2, a novel concern that has surfaced pertains to the secondary infections, predominantly fungal, that are being increasingly identified in patients diagnosed with COVID-19. One such invasive fungal infection that has been garnering attention is mucormycosis, particularly in the context of its cerebrovascular manifestations in patients treated in tertiary care settings^1^,2^.

Mucormycosis, a serious infection instigated by the fungi belonging to the order Mucorales, has traditionally been associated with immunocompromised individuals^3^. This fungal infection is characterized by its rapid progression and high mortality rate, with a notable

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propensity to cause vascular invasion leading to thrombosis and subsequent tissue necrosis^4^. Notwithstanding, the emergence of COVID-19 has notably exacerbated the incidence of mucormycosis, thereby bringing to light the intricate relationship between viral infections and fungal opportunistic pathogens^5^.

Cerebrovascular diseases, encompassing conditions like strokes and transient ischemic attacks, have historically been associated with infectious diseases, demonstrating the profound impact of infections on vascular health^6^. Given the pro-inflammatory and pro-thrombotic state induced by SARS-CoV-2, the virus poses as a potential facilitator for the onset and progression of mucormycosis, particularly accentuating the cerebrovascular complications that are now being witnessed in tertiary care settings^7^.

Tertiary care centers, renowned for their specialization in complex medical conditions, have been at the forefront of managing patients with COVID-19 associated mucormycosis (CAM). These settings necessitate a nuanced approach to both diagnose and manage the cerebrovascular involvements that are being increasingly documented in CAM patients. The management paradigm in these centers involves a multidisciplinary approach, pooling in expertise from neurology, infectious diseases, and critical care specialties to address the complex interplay of COVID-19 and mucormycosis and their cerebrovascular repercussions^8^.

The pathophysiological aspects underlying the cerebrovascular involvements in CAM patients can be multi-pronged. SARS-CoV-2 is known to induce a hypercoagulable state, fostering a milieu that is conducive for the occurrence of thromboembolic events. This, coupled with the vascular invasiveness of mucorales, presents a heightened risk for cerebrovascular complications. Moreover, the concomitant presence of diabetes mellitus, a

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common comorbidity in COVID-19 patients, poses an added risk, given the known association between hyperglycemia and mucormycosis^9^.

The diagnostic protocols in these cases demand a high degree of precision and insight, given the overlap in the radiological and clinical manifestations of COVID-19 and mucormycosis. The cerebrovascular involvement, which often presents as strokes or hemorrhages, requires meticulous monitoring and swift intervention to prevent adverse outcomes. This necessitates the development of adept diagnostic strategies that facilitate early identification and timely management of cerebrovascular complications in CAM patients^10^.

In the burgeoning field of research on this topic, the focus now shifts to forging a deeper understanding through robust scientific inquiries. As it stands, the existing literature predominantly encompasses case reports and smaller cohort studies, providing an initial insight but potentially not portraying the complete picture of the cerebrovascular implications in CAM patients. Therefore, larger cohort studies and randomized controlled trials are essential to develop a comprehensive understanding, enabling healthcare providers to navigate this complex clinical terrain with an evidence-based approach^11^.

In conclusion, the nexus between COVID-19 and mucormycosis delineates a new frontier in the clinical landscape, one that demands an in-depth exploration and analysis, especially concerning cerebrovascular involvements. As the medical community navigates this evolving clinical scenario, the tertiary care centers stand as the vanguard, shouldering the responsibility of developing innovative strategies to mitigate potential cerebrovascular complications. As we forge ahead, the symbiotic relationship between research and clinical practice becomes increasingly indispensable, laying the foundation for a holistic, proactive, and responsive approach to patient care in this domain^12^.

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COVID-19 infection is known to produce a state of hyper inflammation that damages the endothelium and alveoli which is associated with development of opportunistic infections.Mucormycosis is a life-threatening fungal infection that occurs in immunocompromised patients.India has the second highest burden of COVID-19 in the world next to United states, second highest number of diabetic patients and highest prevalence of mucormycosis in the world (140 cases/ million). Mucormycosis was rampant during second wave of COVID-19 pandemic. There was more than 5 fold raise in mucormycosis cases.Prothrombotic state created by COVID-19, along with the angio-invasive nature of the fungus and presence of additional risk factors like diabetes have led to the higher incidence of cerebrovascular involvement and mortality. The present study was conducted to evaluate clinical profile of these patients and to analyse the association of various factors and the survival rates among these patients with cerebrovascular involvement

OBJECTIVES OF THE STUDY

1. To study the demographic data, clinical presentation and laboratory parameters in patients with cerebrovascular involvement in COVID 19 associated mucormycosis.
2. To correlate between various factors and mortality outcomes in these patients.

MATERIALS AND METHODS

Study Design

This cross-sectional study was conducted to investigate the cerebrovascular involvements in patients diagnosed with COVID-19 associated mucormycosis (CAM) at hospitals affiliated with BMCRI. The study spanned from May 2021 to August 2021, during which time pertinent data from 49 patients were meticulously recorded and analyzed.

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Inclusion Criteria

The study embraced patients who were aged above 18 years, willing to provide informed consent, had a prior diagnosis of COVID-19 infection as confirmed by RT-PCR/RAT tests, a concurrent diagnosis of mucormycosis as verified by KOH mount, histopathology of biopsied tissue, or fungal growth in cultures, and evidence of cerebrovascular involvement as indicated in CT scans.

Exclusion Criteria

Individuals were excluded from the study if they were below 18 years of age, unwilling to provide informed consent, did not have a previous COVID-19 diagnosis, or lacked cerebrovascular involvement in the CT scans.

Data Collection

Data collection was a crucial phase in this study. Demographic data such as age, gender, and other pertinent details were meticulously recorded. The clinical presentation, encompassing the various symptoms and manifestations noted at the time of presentation, was documented in detail. A careful note was taken of the specific neurologic symptoms and signs as part of capturing the neurologic manifestations. Existing medical conditions and comorbidities were identified and documented under underlying comorbidities. The extent and severity of the previous COVID-19 infection were assessed, categorized, and documented to discern the severity of the COVID-19 infection. Pertinent laboratory findings were compiled under the section laboratory parameters. All the medical treatments that were administered during the hospital stay were recorded under the medical treatments category. Details regarding any surgical interventions that were undertaken were noted down, encompassing all surgical interventions that were performed.

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Statistical Analysis

The statistical analysis was undertaken using the SPSS (Statistical Package for the Social Sciences) version 20, a product of IBM Corp., Armonk, NY, USA, released in 2011. The initial step in this analysis involved the calculation of descriptive statistics where the explanatory and outcome variables were analyzed. Quantitative variables were described using means and standard deviations, and qualitative variables were represented through frequencies and proportions. Following this, the chi-square test was employed to ascertain the relationship between the outcome and quantitative variables, providing an in-depth understanding of the potential associations and correlations. The independent t-test was utilized as a means to analyze the mean difference between the variables and the outcome of the disease, thus furnishing a comprehensive view of the disease outcomes in the context of the variables analyzed. This careful statistical analysis enabled a meticulous examination of the data, facilitating the drawing of coherent conclusions regarding the cerebrovascular involvement in patients diagnosed with COVID-19 associated mucormycosis.

RESULTS

Table 1: Comparison of outcome of the disease with respect to gender:

Gender	Outcome		Total
	ALIVE	DEATH	
Female	6	6	12
	19.4%	33.3%	24.5%
Male	25	12	37
	80.6%	66.7%	75.5%
Total	31	18	49
	100.0%	100.0%	100.0%

From the data, it is evident that a significantly higher number of male patients were involved in the study (75.5% male vs. 24.5% female). The survival rate among males was considerably higher at 80.6%, compared to 19.4% in females. Furthermore, the death rate in males was slightly lower (66.7%) than in females (33.3%).

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Table 2: Age distribution:

Outcome	N	Age (years)	
		Mean	Std. Deviation
Survived	31	46.81	11.583
Expired	18	59.11	8.072
Total	50	49.3	12.318

The average age of the patients who survived was 46.81 years with a standard deviation of 11.583, whereas the average age of those who expired was notably higher at 59.11 years with a standard deviation of 8.072.

Table 3: Distribution of the comorbidties among the patients with ROCM

	OUTCOME					
	ALIVE		DEATH		Total	
	N	%	N	%	N	%
T2DM	19	61.3%	2	11.1%	21	42.8%
T2DM, INTRAORBITAL NH lymphoma	1	3.2%	0	0.0%	1	2.0%
CKD, ITP, HTN, T2DM	0	0%	1	5.6%	1	2.0%
IHD, CVA, HTN	0	0%	1	5.6%	1	2.0%
LEUKEMIA, SPLEENIC ABSCESS	1	3.2%	0	0.0%	1	2.0%
OLD PTB, T2DM	0	0%	1	5.6%	1	2.0%
T2DM, HTN, IHD	1	3.2%	2	11.1%	3	6.1%
T2DM IHD	2	6.5%	2	11.1%	4	8.2%
T2DM IHD, HERPES LABIALIS	1	3.2%	0	0.0%	1	2.0%
T2DM, HTN	5	16.1%	8	44.4%	13	26.5%
T2DM, HTN, CKD	0	0%	1	5.6%	1	2.0%
T2DM, OLD CVA	1	3.2%	0	0.0%	1	2.0%
TOTAL	31	100%	18	100.0%	49	100.0%

The majority of the participants had diabetes, accounting for 95.9% of the cases, followed by hypertension, which was found in 38.78% of the cases. Various combinations of

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comorbidities were observed, but the high prevalence of diabetes stood out prominently in both survival and death categories.

Table 4: Correlation between usage of steroids in COVID-19 treatment and outcome

		STEROID HISTORY				
		N	y	Y	Total	p-value
OUTCOME	ALIVE	23	0	8	31	0.000
	DEATH	0	3	15	18	
Total		23	3	23	49	

A significant correlation was observed between the history of steroid use and the outcome (p-value = 0.000), where those who had used steroids experienced a higher mortality rate.

Table 5: Correlation between the of duration of diabetes, duration of steroids and the survival rate

Variables	OUTCOME	N	Mean	Std. Dev	Mean Difference	p value*
Duration of Diabetes	ALIVE	31	4.58	7.22	-9.81774	0.000
	DEATH	18	14.4	7.33		
DURATION OF STEROIDS IN DAYS	Survived	31	1.61	3.008	-9.887	0.000
	Expired	18	11.5	2.526		

*Independent t test

Both the duration of diabetes and the duration of steroid use were significantly associated with mortality, with p-values of 0.000 in both cases, indicating a strong positive correlation with the outcome.

Table 6: Clinical presentation of patients with ROCM:

Symptoms	Outcome		Total
	Survived	Expired	
Nasal block	22	8	30
	59.50%	61.50%	60.00%
Nasal discharge	24	8	32

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	64.90%	61.50%	64.00%
Headache	32	11	43
	86.50%	84.60%	86.00%
Vision loss	22	8	30
	59.50%	61.50%	60.00%
Facial pain	25	8	33
	67.60%	61.50%	66.00%
Facial swelling	26	8	34
	70.30%	61.50%	68.00%

The most common symptom observed was a headache (86%), followed by motor weakness (83.67%). Altered sensorium was presented in 20.4% of the cases. A variety of CNS symptoms were documented, with motor weakness being prevalent.

Table 7: CNS symptomswith outcomes

CNS SYMPTOMS	OUTCOME					
	ALIVE		DEATH		Total	
	N	%	N	%	N	%
FACIAL NERVE PALSY, INVOLUNTARY MOVEMENTS, MOTOR WEAKNESS	0	0.0%	1	5.6%	1	2.0%
MOTOR WEAKNESS	19	61.3%	6	33.3%	25	51.0%
MOTOR WEAKNESS, ALTERED SENSORIUM	1	3.2%	7	38.9%	8	16.3%
MOTOR WEAKNESS, APHASIA	3	9.7%	0	0.0%	3	4.1%
MOTOR WEAKNESS, ATAXIA	0	0.0%	1	5.6%	1	2.0%
ALTERED SENSORIUM	1	3.2%	1	5.6%	2	4.1%
ALTERED SENSORIUM, MOTOR WEAKNESS	1	3.2%	1	5.6%	2	4.1%
ASYMPTOMATIC	6	19.4%	0	0.0%	6	12.2%
SWAYING, IMBALANCE, MOTOR WEAKNESS	0	0.0%	1	5.6%	1	2.0%
	31	100.0%	18	100.0%	49	100.0%

Most of the patients had presented with multiple symptoms. Most common CNS symptom was headache (86%) followed by motor weakness (83.67%). 10 patients (20.4%) presented with altered sensorium.

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Table 8: Correlation between the disease outcome and the clinical examination

Examination findings	Outcome		Total	p value
	Survived	Expired		
	13	8	21	
Palatal involvement	35.10%	61.50%	42.00%	0.097
	20	6	26	
Proptosis	54.10%	46.20%	52.00%	0.624
	27	8	35	
EOM restriction	73.00%	61.50%	70.00%	0.439
	25	10	35	
Abnormal vision	67.50%	77%	70%	0.526

There was no significant correlation found between different clinical examination findings (like palatal involvement, proptosis, EOM restriction, abnormal vision) and the outcome, with p-values ranging from 0.097 to 0.624.

Table 9: Correlation between the type of sinus involved and the survival rate of ROCM

Types of sinus involved	Outcome		Total	p value
	Survived	Expired		
	35	12	47	
Maxillary	94.60%	92.30%	94.00%	0.765
	34	12	46	
Ethmoid	91.90%	92.30%	92.00%	0.962
	23	7	30	
Frontal	62.20%	53.80%	60.00%	0.599
	30	8	38	
Sphenoid	81.10%	61.50%	76.00%	0.156
	31	9	40	
Orbit	83.80%	69.20%	80.00%	0.259

There was no significant association found between the involvement of the sinus and the survival rate of the study population.

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Table 10. Spectrum of Cerebrovascular involvement:

	OUTCOME				Total	
	ALIVE		DEATH			
	N	%	N	%	N	%
ARTERIAL INFRACT	28	90.30%	11	61.10%	39	79.60%
Cavernous sinus thrombosis	14	45.20%	9	50.00%	23	46.90%
ARTERIAL INFRACT WITH CST	11	35.50%	2	11.10%	13	26.50%
CVA with cerebral abscess	9	29.03%	7	38.89%	16	32.65%
CVA with meningitis	2	6.45%	3	16.67%	5	10.20%

The data showcases the various cerebrovascular involvements observed in patients, with arterial infarct being the most prevalent, seen in 79.6% of cases.

Table 11: Correlation between the type of fungus and the clinical outcome.

	OUTCOME					
FUNGAL C/S	ALIVE		DEATH		Total	
	N	%	N	%	N	%
ASPERGILLUS FLAVUS	1	3.2%	0	0.0%	1	2.0%
ASPERGILLUS FUMIGATUS	1	3.2%	1	5.6%	2	4.1%
MUCOR	20	64.5%	11	61.1%	31	63.3%
MUCOR AND ASPERGILLUS FUMIGATUS	1	3.2%	2	11.1%	3	6.1%
NEG	8	25.8%	4	22.2%	12	24.5%
	31	100.0%	18	100.0%	49	100.0%

There was no significant difference found between the type of fungus affecting the patients and the survival rate. Most common fungus found on HPE mount was mucor with the prevalence of 64% and the least common were aspergillus, mucor with aspergillus was found in 3 patients

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Table 12: Correlation between the outcome of ROCM and the operation required.

	OUTCOME					
OPERATED	ALIVE		DEATH		Total	
	N	%	N	%	N	%
NO	1	3.2%	1	5.6%	2	4.1%
YES	30	96.8%	17	94.4%	47	95.9%
	31	100.0%	18	100.0%	49	100.0%

There was no correlation between the patients who had operated and those who were managed with conventional COVID protocol for mucor cases.

Table 13: Correlation between the Lab parameters and the survival rate of ROCM patients

Variables	OUTCOME	N	Mean	Std. Dev	Mean Difference	p value*
HB	Survived	31	11.44	1.58	0.5387	0.254
	Expired	18	10.80	1.47		
TC	Survived	31	10,065.16	4,116.83	-1267.783	0.310
	Expired	18	11,343.31	4,211.61		
CRP	Survived	31	32.16	10.27	-95.65038	0.000
	Expired	18	125.6	45.12		
D DIMER	Survived	31	321.39	88.28	-510.502	0.000
	Expired	18	831.81	151.19		
LDH	Survived	31	156.03	20.47	-177.9455	0.000
	Expired	18	334.29	70.63		
HBA1C	Survived	31	7.87	1.254	-3.9440	0.000
	Expired	18	11.89	1.248		
UREA	Survived	31	21.703	16.207	-9.3801	0.111
	Expired	18	33.044	25.07		
CREATININE	Survived	31	3.97	1.76	2.59943	0.537
	Expired	18	1.48	0.52		
ALB	Survived	31	3.08	0.53	0.2163	0.147
	Expired	18	2.89	0.44		

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There was significantly higher level of D dimer, HbA1c, CRP and LDH among the recruited study population and the mortality was significantly higher among those who had higher level of D dimer, HbA1c, CRP and LDH.

Table 14: Correlation between severity of COVID-19 as requirement of O2 supplementation with outcome:

		O2 HISTORY			P value
		No	Yes		
OUTCOME	ALIVE	21	10	31	0.000
	DEATH	1	17	18	0.000
Total		22	27	49	

Among the mortality group 88% had a history of moderate to severe form of COVID-19 infection requiring O2 supplementation as compared to 32.26% among survived group which was statistically significant.

DISCUSSION

The emergence of Rhino-orbital-cerebral mucormycosis (ROCM) in the post-COVID-19 scenario has caused significant concerns due to its alarming morbidity and mortality. This study offers a comprehensive assessment of various clinical, laboratory, and imaging parameters and their potential correlation with the outcome of the disease.

One of the prominent findings from our study was the predominance of ROCM among male patients. Our findings showed a substantial male preponderance with 75.5% being male and a higher survival rate among males (80.6%) compared to females. This gender disparity is consistent with the study conducted by Sharma et al. (2021), where they noted a higher prevalence among males (70%).[13] However, contrastingly, in a study by Gupta et al. (2019), the gender distribution was almost equal.[14]

Age-wise, the mean age of patients who expired was considerably higher at 59.11 years. This is in line with the findings of Mehta et al. (2022), which suggested that older age was a

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significant predictor for mortality in ROCM, with a mean age of 60.5 years in the non-survival group.[15] The relationship between age and poorer outcomes in various diseases, especially infectious ones, is well documented, attributing to a diminished immune response with aging.[16]

The comorbid presence of diabetes in our study group was strikingly high at 95.9%. Previous studies have also highlighted the role of diabetes, particularly uncontrolled diabetes, in the manifestation of ROCM.[17] The underlying hyperglycemic environment is conducive for fungal growth, combined with a diminished immune response, making diabetics more susceptible to infections.[18] Our data aligns well with the findings of Kumar et al. (2021), who found that 94% of their ROCM cohort had diabetes.[19]

Steroid usage has been a contentious issue in the backdrop of the COVID-19 pandemic. Our findings depicted a significant correlation between the history of steroid use and increased mortality (p-value = 0.000). This resonates with the concerns raised by Rajan et al. (2021), who emphasized the potential risk of opportunistic infections, like ROCM, following indiscriminate steroid use.[20]

Although mucor was the most commonly identified fungus in our study (64%), the outcomes did not significantly differ based on the fungal type. This stands in contrast to the study by Patel et al. (2018), where they found aspergillus-associated ROCM to have a higher mortality.[21]

While laboratory parameters like D-dimer, HbA1c, CRP, and LDH demonstrated significant variations between the groups, the most salient finding was the direct correlation between the severity of COVID-19 (inferred from O2 requirements) and poor outcomes in our cohort (p-value=0.000). This is supported by the observations made by Sen et al. (2022), wherein the

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severity of the antecedent COVID-19 infection significantly influenced the progression and prognosis of secondary infections, including ROCM.[22]

In conclusion, the interplay of various factors like age, gender, comorbidities, especially diabetes, steroid use, and the severity of COVID-19, largely dictate the outcome in ROCM patients. Our study offers invaluable insights, but continuous research is imperative given the evolving nature of the disease and its determinants.

CONCLUSION

The present study illumines the pivotal role of demographic factors in influencing the prevalence and severity of ROCM. A conspicuous gender disparity and heightened vulnerability in the age bracket of 50-60 necessitate targeted medical interventions[13,15]. Moreover, the intricate interplay between diabetic conditions and ROCM severity calls for heightened vigilance and management strategies in diabetic individuals[17,19]. The discernment of the differential clinical outcomes between Mucor and Aspergillus infections posits a novel trajectory for future research and clinical approaches[21]. Collectively, the study heralds a paradigm shift in ROCM management, steering towards a demographic-focused approach in combating the disease. Further investigations are warranted to fortify these findings and foster the development of efficacious clinical strategies.

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