

# A retrospective review to assess the clinical outcome of rhino-orbito-cerebral mucormycosis patients with COVID-19 infection and its association with glycaemic control

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## Abstract

**Introduction:** The coronavirus disease 2019 (COVID-19) pandemic in India, having caused 29 500 000 confirmed cases and 374 000 deaths as of June 14, 2021, continues to have devastating consequences, including a large epidemic of COVID-19-associated mucormycosis (COVID-Mucor), manifesting as rhino-orbito-cerebral mucormycosis (ROCM), which has worsened the morbidity among vulnerable populations (JHU, 2021) <sup>1</sup>. Reports have shown a much larger surge in the incidence of COVID-Mucor during the second wave in 2021 than during the first wave (Patel *et al.*, 2021; Moorthy *et al.*, 2021) <sup>2,3</sup>. This rapid rise in COVID-Mucor is probably caused by several factors. For patients with diabetes mellitus, lockdowns, travel restrictions, and restricted access to medical care have worsened glycaemic control, the central risk factor for ROCM in India (Chakrabarti *et al.*, 2006) <sup>4</sup>. Addressing these could reduce morbidity and mortality among vulnerable populations.

**Material and Methods:** A Retrospective chart review was conducted in Department of General medicine Dr S N Medical College Jodhpur among population included all rhino-orbito-cerebral mucormycosis patients with Covid-19 infection who were admitted in Mucormycosis ward, Dr S N Medical College Jodhpur from Oct. 2020 to Sept 2021. Bed head tickets of all these patients were reviewed. The final outcome was noted from the bed head ticket, the outcome was correlated with random blood sugar and HbA1c level at admission.

**Conclusion:** Mucormycosis is angioinvasive fungal disease with significant morbidity and mortality. The disease has risen dramatically due to interplay of COVID 19 pandemic, uncontrolled diabetes and inappropriate corticosteroid use leading to pathogenic invasion and adverse outcomes. The treatment involves early detection, surgical debridement and antifungal drugs for better survival. Our study revealed an evident role of hyperglycemia as major risk factor for mucormycosis infection. Those patients who had HbA1c > 10 could not survive inspite of best treatment and those patients who survived their hospital stay was directly proportional to their HbA1c level. All those patients who had cerebral involvement

could not be saved. Hence, we suggest that closely tracking the levels of blood sugar in COVID-19 patients is a valuable tool to stratify the risk that a patient will have mucormycosis.

**Keywords:** COVID 19, Mucormycosis, HB1AC

## **Introduction**

### **Background**

Mucormycosis (previously called zygomycosis) is a rare but serious angio-invasive infection caused by a group of fungi called mucormycetes. Spores of these ubiquitous fungi (commonly found in soil, fallen leaves, compost, animal dung and air) can be inhaled and then infect the lungs, sinuses, and extend into the brain and eyes. Less often, infection may develop when the spores enter the body through a cut or an open wound. Mucormycosis is not a contagious disease, it cannot be spread from one person to another <sup>[5]</sup>. Mucormycosis mainly affects people who are immunocompromised, or patients already infected with other diseases. High risk groups include people with diabetes (especially diabetic ketoacidosis), solid organ transplantation, neutropenia (low neutrophils), long-term systemic corticosteroid use and hemochromatosis. The risk is high for people living with HIV and those using immunomodulating drugs and anti-fungal voriconazole in some high-risk groups <sup>[6]</sup>. The incidence rate of mucormycosis globally varies from 0.005 to 1.7 per million population. In India, prevalence of mucormycosis is estimated as 140 per million population, which is about 80 times higher than the prevalence in developed countries <sup>[7]</sup>.

Clinical presentation is classified according to the organ involvement. It can be rhino-orbital cerebral, pulmonary, cutaneous, gastrointestinal or disseminated. Mucormycosis is an aggressive, life-threatening infection requiring prompt diagnosis and early treatment. Treatment usually consists of antifungal medications and surgery <sup>[8]</sup>.

Following the surge of COVID-19 associated mucormycosis and the Government of India directive, several states in India made mucormycosis a notifiable disease in May 2021. This will provide better insights into the disease burden, population characteristic, risk factors, clinical spectrum and outcomes of these patients <sup>[9]</sup>. Diabetes is the most common metabolic disorder and is an independent risk factor for Severe COVID-19 and Mucormycosis. In patients with diabetes affected with COVID-19 super infection with Mucormycosis will lead to adverse clinical outcome and prolonged hospital stay. This study aims to study the clinical spectrum of Mucormycosis in patients with COVID-19 and diabetes and their subsequent outcomes <sup>[10]</sup>. HbA1c is measured primarily to determine the three-month average blood sugar level and can be used as a diagnostic test for diabetes mellitus and as an assessment test for glycemic control in people with diabetes.

## **Material and Methods**

**Study design:** Retrospective chart review.

**Study place:** Department of General medicine Dr S N Medical College Jodhpur.

**Study population:** Population included all rhino-orbito-cerebral mucormycosis patients with Covid-19 infection who were admitted in Mucormycosis ward, Dr S N Medical College Jodhpur. Bed head tickets of all these patients were reviewed.

**Study period:** All the patients of rhino-orbito-cerebral mucormycosis with Covid-19 infection admitted from Oct. 2020 to Sept 2021 were recruited.

**Sample size:** All rhino-orbito-cerebral mucormycosis with Covid-19 infection patients admitted in Mucormycosis ward Dr S N Medical College Jodhpur during study period.

**Inclusion criteria:** All rhino-orbito-cerebral mucormycosis positive cases with history of covid-19 infection admitted in Department of Medicine in Mucormycosis ward Dr S N Medical College, Jodhpur.

**Methodology:** After ethical clearance from institutional ethical committee, bed head tickets of all rhino-orbito-cerebral mucormycosis patients were reviewed. The demographic profile including age, sex, residence was noted in performa similarly clinical profile will be noted which include date of admission, duration of hospitalization, any co-morbidity and any risk factors (diabetes, HIV, obesity, history of steroid intake), treatment given during hospitalization, any complications developed during hospitalization. The final outcome was noted from the bed head ticket, the outcome was correlated with random blood sugar and HbA1c level at admission. Diabetes Mellitus was considered as per ADA criteria <sup>[11]</sup>.

**Criteria for the diagnosis of rhino-orbito-cerebral mucormycosis:** A positive case of rhino-orbito-cerebral mucormycosis was called when a positive KOH mount comes from biopsy or scrapping from rhino-orbito-cerebral mucormycosis.

### Data analysis

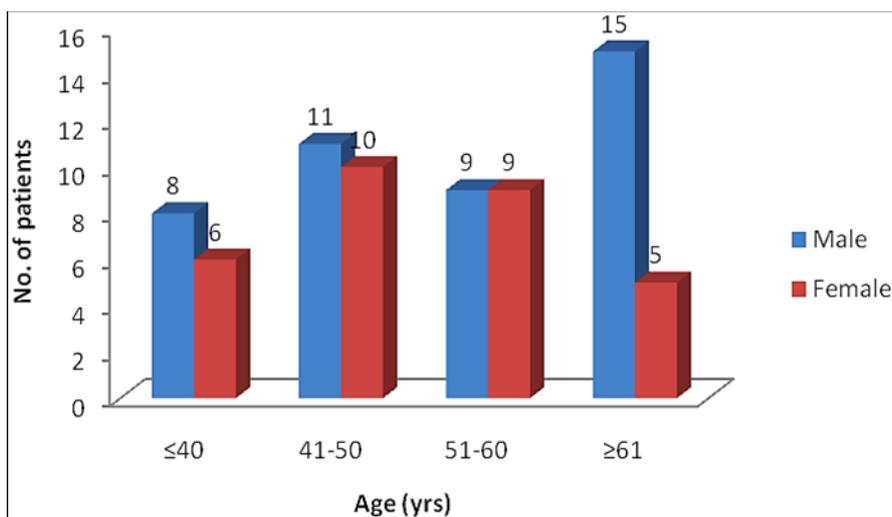
Data collected during the study was compiled using Microsoft Excel spreadsheets. Data analyzed statistically using the Med Calc Statistical Software version 19.3 for Windows edition. Data were presented as mean  $\pm$  standard deviation (SD) for normally distributed quantitative variables. Comparison between the groups was done by  $\chi^2$ -test and t test. A p value of  $< 0.05$  was considered as statistically significant.

### Results

**Table 1:** Age and Gender Distribution of Patients

Age (yrs)	Male		Female		Total	
	N	%	N	%	N	%
$\leq 40$	8	57.14	6	42.86	14	19.18
41-50	11	52.38	10	47.62	21	28.77
51-60	9	50.00	9	50.00	18	24.66
$\geq 61$	15	75.00	5	25.00	20	27.40
Total	43	58.90	30	41.10	73	100.00

Table 1 shows age wise distribution of study population. 14 (19.178%) subjects were less than  $\leq 40$  years of age. 21 (28.77%) subjects were in the age group of 41-50 years. 18 (24.66%) were in the age group of 51-60 years of age and 20 (27.40%) were in the age group of  $> 61$  years of age. The mean age was 52.43 years.

**Table 2:** Involvement of Paranasal Sinuses

Nasal	No. of patients	Percentage
Maxillary	67	91.78
Facial	28	38.36
Ethmoidal	45	61.64
Sphenoidal	32	43.84

In present study most common paranasal sinus involved 67(91.78%) was maxillary, followed by ethmoidal 45(61.64%), sphenoidal 32 (43.84) and facial 28(38.36%). We found involvement of multiple sinuses in single patients. 16 Patients had 2 sinuses involvement, 7 Patients had 3 and 21 Patients had all 4 sinuses involvement.

**Table 3:** Distribution of Site of Involvement

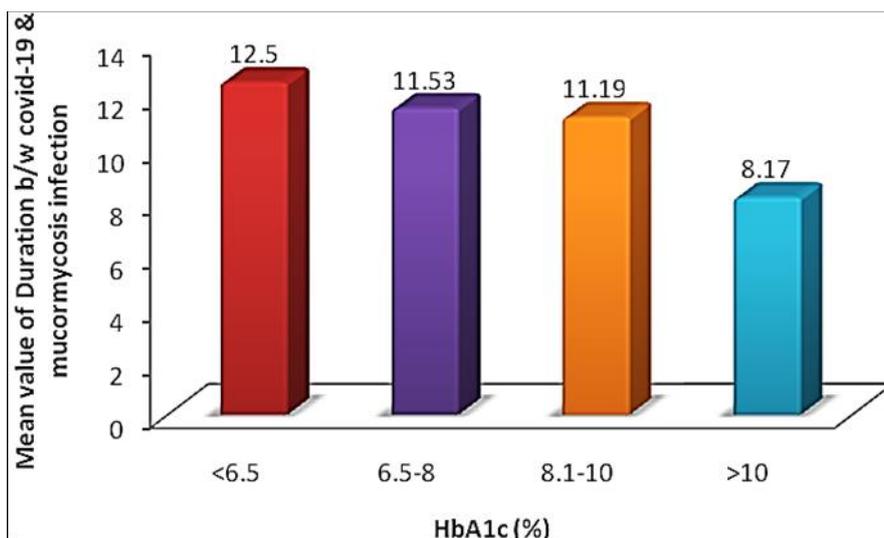
Site of involvement	No. of patients	Percentage
Orbital	18	24.66
Cerebral	5	6.85
Nasal	73	100.00

In present study most common site involved 73(100.00%) was nasal, however in addition orbital involvement was in 18 (24.66%) and cerebral 5 (6.85%).

**Table 4:** Correlation Between HbA1c with Duration Between Covid-19 and Mucormycosis Infection

HbA1c (%)	Duration b/w covid-19 & mucormycosis infection			p value
	No. of patients	Mean	SD	
<6.5	12	12.5	5.9	0.0001
6.5-8	13	11.53	3.98	
8.1-10	20	11.19	1.48	
>10	28	8.17	2	

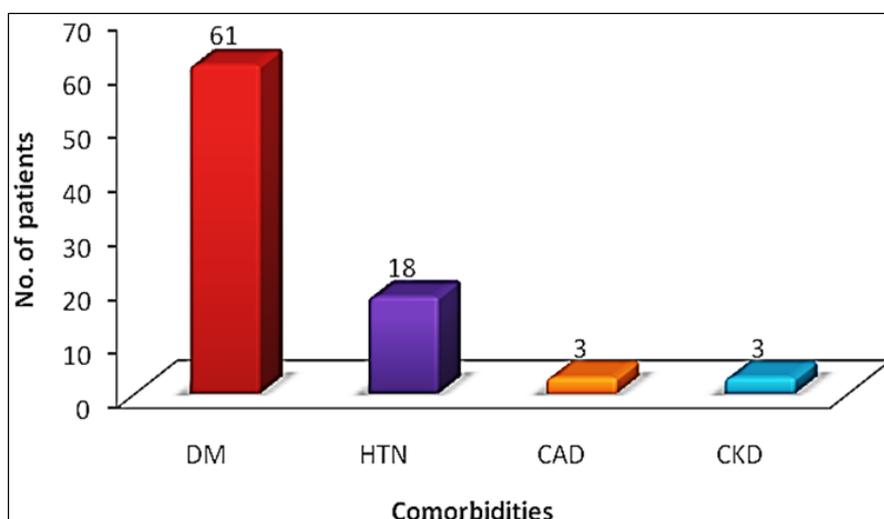
In present study as the HbA1c level increases the duration between covid-19 and mucormycosis infection decreases. There was significant difference HbA1c with duration b/w covid-19 & mucormycosis infection.



**Table 5:** Distribution of Comorbidities

Comorbidities	No. of patients	Percentage
DM	61	83.56
HTN	18	24.66
CAD	3	4.11
CKD	3	4.11

In present study most common comorbidity 61(83.56%) was diabetes mellitus, followed by hypertension 18 (24.66%) and 3 (4.11%) patients coronary artery disease and chronic kidney disease respectively. No patients of type I DM was admitted with mucormycosis.

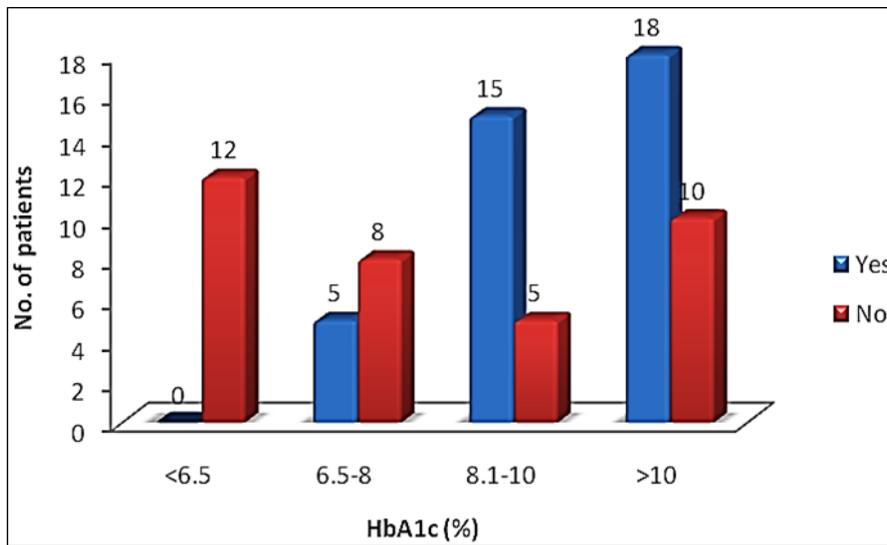


**Table 6:** Correlation Between HbA1c With Diabetes Mellitus

HbA1c (%)	Past h/o DM				Total	
	Yes		No			
	N	%	N	%	N	%
<6.5	0	0.00	12	100.00	12	16.44
6.5-8	5	38.46	8	61.54	13	17.81
8.1-10	15	75.00	5	25.00	20	27.40
>10	18	64.29	10	35.71	28	38.36
Total	38	52.05	35	47.95	73	100.00

Chi square 19.88, P value 0.0002 (S)

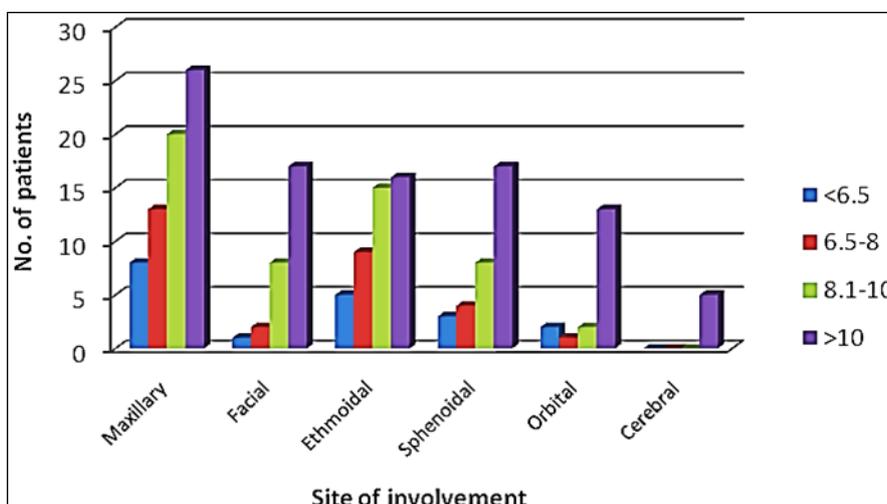
In present study 38 (52.05%) patients had raised HbA1c with past h/o diabetes mellitus and 23 (31.50%) had raised HbA1c with no previous history of diabetes mellitus.



**Table 7:** Correlation between Site of Involvement with HbA1c

Site of involvement	HbA1c (%)								Total	
	<6.5		6.5-8		8.1-10		>10			
	N	%	N	%	N	%	N	%	N	%
Maxillary	8	11.94	13	19.40	20	29.85	26	38.81	67	91.78
Facial	1	3.57	2	7.14	8	28.57	17	60.71	28	38.36
Ethmoidal	5	11.11	9	20.00	15	33.33	16	35.56	45	61.64
Sphenoidal	3	9.38	4	12.50	8	25.00	17	53.13	32	43.84
Orbital	2	11.11	1	5.56	2	11.11	13	72.22	18	24.66
Cerebral	0	0.00	0	0.00	0	0.00	5	100.00	5	6.85

In present study maximum maxillary sinus was involved 67 (91.78), in which 8 (11.94%) were <6.5 HbA1c followed by 13 (19.40%) were 6.5-8 HbA1c, 20 (29.85%) were 8.1-10 HbA1c and 26 (38.81%) were >10 HbA1c. All patients of cerebral involvement had HbA1c >10.

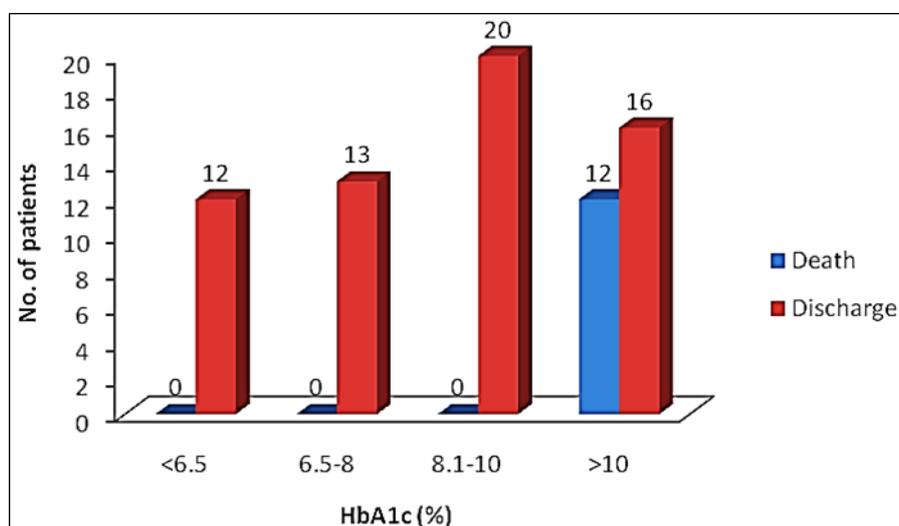


**Table 8:** Correlation between HbA1c with Outcome

HbA1c (%)	Death		Discharge		Total	
	N	%	N	%	N	%
<6.5	0	0.00	12	100.00	12	16.44
6.5-8	0	0.00	13	100.00	13	17.81
8.1-10	0	0.00	20	100.00	20	27.40
>10	12	42.86	16	57.14	28	38.36
Total	12	16.44	61	83.56	73	100.00

Chi square 23.08, P value <0.0001 (S)

In present study all patients with HbA1c in  $\leq 10$  have recovered and discharged. 12 (42.86%) patients expired and 16 (57.14%) were discharged among  $>10$  HbA1c. There was significant difference in HbA1c with outcome.



## Discussion

In our retrospective study clinical outcome of rhino-orbital-cerebral mucormycosis with covid-19 infected patients in relation to glycosylated hemoglobin level, included all rhino-orbital-cerebral mucormycosis patients with Covid-19 infection who were admitted in Mucormycosis ward, Dr S N Medical College Jodhpur from Oct. 2020 to Sept 2021 were recruited. Rhino-orbital mucormycosis is an aggressive fungal opportunistic infection of the immune-compromised and debilitated patients. The ubiquitous, naturally occurring fungus presents as a rhino-orbital cerebral infection in those with weak innate immunity to fight the external invading pathogen. An early diagnosis with a prompt, well-coordinated, multidisciplinary approach has been vital to save both the life and sight of the patient. Microbiological diagnosis, control of the underlying systemic condition, and antimicrobial therapy with debridement of necrotic tissue have remained the mainstay of management of rhino-orbital mucormycosis over the years. Exenteration may not be absolutely necessary if well managed<sup>[38]</sup>. In their study, a large institutional cohort of rhino-orbital mucormycosis in the present COVID-19 ongoing pandemic was seen. The demographic profile of the patients was similar to those reported in the world literature. The mean age of presentation was 56.3 years with a skew deviation toward the male gender (64.5%) vis-à-vis females (35.5%). The most common systemic risk factor was uncontrolled diabetes (96.7%). COVID-19 positivity and concurrent steroid use further decreased the immunity in 61.2% of patients. In our study 43(58.90%) were males and 30(41.10%) were females and the mean age was 52.43 years (Table 1 & 2). Which is concomitant Teny M John *et al*<sup>[12]</sup> uncontrolled diabetes mellitus

and severe covid-19 converge the perfect storm for mucormycosis, where there are total 43 patients with male predominant 34 (83%) and mean age was 55 years. Another study concluded by Mishra Y *et al.* <sup>[10]</sup> diabetes covid-19 and mucormycosis-clinical spectrum and outcome in a tertiary medical centre in Western India, where there were 32 patients with 53.1% male predominant and mean age of 58.28 years.

In our study most common comorbidity 61 (83.56%) was diabetes mellitus, followed by hypertension 18 (24.66%) and coronary artery disease 3 (4.11%). Which is concomitant Mishra Y *et al.* <sup>[10]</sup>, where diabetes mellitus was most common 28 (87.5%) comorbidity, followed by hypertension 16 (50%). Other study were also having similar finding such as Teny M John *et al.* <sup>[12]</sup>, Bhanuprasad K *et al.* <sup>[13]</sup>.

In our study most common site involved 73(100.00%) was nasal, followed by orbital 18 (24.66%) and cerebral 5 (6.85%), which is concomitant with Bhanuprasad K *et al.* <sup>[13]</sup> where there are 132 patients studied and all had nasal involvement.

In our study most common paranasal sinus involved 67(91.78%) was maxillary, followed by ethmoidal 45(61.64%), sphenoidal 32 (43.84) and facial 28(38.36%), which is concomitant Mishra Y *et al.* <sup>[10]</sup>, where there is maxillary sinus 28 (87.5%) was the most common paranasal sinus involved followed by ethmoidal 28 (87.5%). In our study mean HbA1c of total population was 9.32%, which is concomitant with Bhanuprasad K *et al.* <sup>[13]</sup> where there was mean HbA1c of 10.84% and Mishra Y *et al.* <sup>[10]</sup> where there was mean HbA1c of 9.06% and Teny M John *et al.* <sup>[12]</sup> where there was mean HbA1c of 10%. In our study all patients discharged with HbA1c in  $\leq 10\%$  (Table 14). 12 (42.86%) were expired and 16 (57.14%) were discharged in  $>10$  HbA1c. There was significant difference in HbA1c value with outcome. Which is concomitant Mishra Y *et al.* <sup>[10]</sup> where mean HbA1c in discharged patients was 8.6% and expired patients it was 12.5%. In our study 38 (52.05%) patients had h/o diabetes mellitus and 23 (31.50%) patients were newly diagnosed to have diabetes mellitus. which is not concomitant with Gupta R *et al.* <sup>[14]</sup> where there was uncontrolled diabetes 85.2% and newly diagnosed diabetes mellitus in 13.9% patients. Probably due to different sample size. In our study as the HbA1c level increases the duration between covid-19 and mucormycosis infection decreases and it was found to be significant difference p value 0.0001 and mean duration b/w covid-19 & mucormycosis infection was 10.50 days. In Teny M John *et al.* <sup>[12]</sup> study mucormycosis diagnosis mean was 22 days.

## Conclusion

In our study clinical outcome of rhino-orbital-cerebral mucormycosis with covid-19 infected patients in relation to glycosylated hemoglobin level was assessed. It included 73 rhino-orbital-cerebral mucormycosis patients confirmed by histopathology with Covid-19 infection who were admitted in Mucormycosis ward, Dr S N Medical College Jodhpur from Oct. 2020 to Sept 2021 were recruited. Majority of patients 43(58.90%) were males. Majority of patients 21 (28.77%) were in the age group of 41-50years. The mean age was 52.43 years. Most common comorbidity 61(83.56%) was diabetes mellitus. Mean HbA1c in discharged patients was 8.67% and in expired patients was 12.62%. All patients were having nasal involved and in some patients there were involvement of multiple sites. Most common paranasal sinus involved 67(91.78%) was maxillary. Out of 73 patients 12 (16.44%) expired, and 61 (83.56%) patients discharged. Most common comorbidity 61(83.56%) was diabetes mellitus, out of 61 patients with Diabetes mellitus 12 (19.67%) patients expired and 49 (80.33%) were discharged. Most common age group affected was 41-50 year, among them 8 (28.57%) patients had HbA1c $>10\%$ . As the HbA1c level increases the duration between admission and discharge also increases. As the HbA1c level increases the duration between covid-19 and onset of mucormycosis infection decreases. Hence, we suggest that closely tracking the levels of blood sugar in COVID-19 patients is a valuable tool to stratify the risk that a patient will have mucormycosis.

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