Original Research Paper

Volume - 12 | Issue - 03 | March - 2022 | PRINT ISSN No. 2249 - 555X | DOI : 10.36106/ijar

Internal Medicine

A STUDY ON THE GLYCEMIC STATUS AND OUTCOME OF PATIENTS WITH COVID ASSOCIATED MUCORMYCOSIS.

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ABSTRACT **Background:**A surge of mucormycosis during the second wave of COVID intrigued the doctors in India to look for the epidemiology of the illness.Diabetes is the most common risk factor for mucormycosis.COVID can cause hyperglycemia due to various reasons.In this study,we describe the outcome of post COVID mucormycosis with respect to the glycemic status of the patient.**Objectives:**(1)To describe the glycemic parameters of patients with COVID-19 Associated Mucormycosis.(2)To describe the one month outcome of the patients.(3)To compare patients with Newly Diagnosed Diabetes Mellitus Post COVID-19 and patients having pre-existing diabetes mellitus.**Methodology:**75 patients with probable or proven mucormycosis with history of COVID atleast 2 weeks before were randomly selected from the mucor ward of Rajiv Gandhi Government General Hospital and their glycemic profile assessed.They were followed up for one month and the results were statistically analyzed.**Results:**Regarding the prior COVID illness,patients had a median hospital stay of 7 days,received 5 days of intravenous steroids and 3.48 days of supplemental oxygen.Patients who had hyperglycemia during COVID also had statistically significantly higher iv steroid use and higher need for oxygen.There was a statistically very significant($p<0.001$) increase in the number of diabetics post COVID(from 57.3% prior to COVID to 90.7% post COVID).Majority of the Mucormycosis patients(69.3%) had severe hyperglycemia during presentation.Pre-existing diabetics had a statistically significant higher incidence of sepsis and renal failure during treatment for mucormycosis.Otherwise,there was no significant difference in outcome between various grades of severity of hyperglycemia,and no distinction was found between pre-existing diabetics and newly diagnosed diabetics.

KEYWORDS : Mucormycosis,post covid diabetes,glycemic status

INTRODUCTION:

The SARS Cov 2 virus is a novel corona virus causing severe acute respiratory syndrome, isolated in Wuhan causing the pandemic the world hasn't seen after the Spanish flu. During the second wave of covid 19 many states in India faced an epidemic of mucormycosis (Covid Associated Mucormycosis ,CAM). Diabetes is the most common risk factor for mucormycosis in most reported series [1,2,3]. COVID 19 is said to cause dysglycemia due to three reasons: stress hyperglycemia, due to steroids given and as an endocrine manifestation of COVID itself [4], making the patients immunoc ompromised and thereby prone to mucormycosis infections. Mucormycosis is an angio-invasive fungal infection, associated with high morbidity and mortality. Identifying characteristics in COVID patients which predispose them to mucormycosis is essential to have a watchful expectancy on COVID Associated Mucormycosis. In this study, we seek to describe the clinical severity and outcome parameters of post COVID mucormycosis with respect to the glycemic status of the patient. We have given importance to a cohort of patients called 'Newly Diagnosed Diabetes During or Post COVID' throughout our discussion.

AIMS & OBJECTIVES:

Primary objective :

(1) To describe the glycemic parameters at admission (FBS, PPBS, HbA1c, presence of hyperglycemia with or without acidosis) of the patients with COVID Associated Mucormycosis.

(2) To describe the one month outcome of the patients in terms of mortality, systemic or cerebral spread and correlate it with the glycemic status.

Secondary objective :

(1) To compare the subset of patients with newly diagnosed Diabetes Mellitus During or Post COVID-19 with patients having pre-existing diabetes mellitus

MATERIALS AND METHODS:

INCLUSION CRITERIA:

Hospitalized patients of any age and gender who met the criteria of

1. Probable or proven mucormycosis. The definitions of probable and proven mucormycosis was in accordance with the DME mucormycosis guidelines, May 2021 [5].
   A. Probable mucormycosis was defined when MRI/CT/ nasal endoscopic evidence suggested mucormycosis.
   B. Proven mucormycosis was defined when there was a microbiologically confirmed case of mucormycosis.
2. Post COVID-19 was defined as atleast 2 weeks following RT-PCR positivity for SARS-CoV.
3. Patients with or without history of diabetes mellitus were included.
4. Patients with other comorbidities maybe included unless exclusion criteria were met.

EXCLUSION CRITERIA:

1. Not willing to participate in study
2. Hb less than 10 g%
3. Pregnancy or breastfeeding mothers
4. COVID-19 and mucormycosis diagnosed at the same time during admission.

Data collection and analysis:

The patients (75) enrolled in the study had detailed clinical history documented. Special focus were given to the symptoms of his/her COVID illness, duration of stay in hospital for COVID-19, duration and type of any oxygen supplementation given, duration and type of steroid given, time interval between discharge from COVID-19 illness and admission for mucormycosis and symptoms pertaining to mucormycosis. Past history was focussed on the duration of pre-existing diabetes mellitus, therapy for diabetes, diabetic management during COVID illness.The above details were collected from the patient and were also cross-verified with their discharge summaries. Clinical examination was focussed on the organ systems affected by mucormycosis. Complete blood count, RFT, LFT, Electrolytes, FBS,

PPBS, admission CBG, HbA1c, ABG, Urine acetone, Urine routine examination were done during admission and repeated as necessary based on the clinical status of the patient. The patients were followed up for 1 month after the date of admission for mucormycosis, for mortality, systemic involvement, cerebral involvement, sepsis, etc.

The data collected were entered and analysed in MS Excel software. The mean FBS, PPBS, HbA1c were calculated.

The patients were classified based on the glycemic status into differtent sub-categories as follows :

(1) Patients with euglycemia (RBS or CBG <200 or HbA1c <6.5) on admission.
(2) Patients with hyperglycemia (RBS or CBG>200 or HbA1c >6.5) on admission
(3) Patients with severe hyperglycermia (HbA1c >10 g/dl) on admission
(4) Patients with Diabetic Keto Acidosis (urine acetone positivity, Glucose >300) on admission
(5) Patients with Diabetes Diagnosed during or after COVID-19 infection.
(6) Patients with history of diabetes mellitus prior to the diagnosis of COVID-19 infection.

The patients were followed up and the outcome parameters were assessed in the above said categories separately.

The sub-category of newly diagnosed Diabetes During or Post COVID were compared with those with pre-existing diabetes mellitus, in terms of COVID related, history, time interval between COVID-19 and mucormycosis, severity of COVID-19, severity of mucormycosis and difference in outcome.

The outcome were measured in terms of :

(1) Mortality
(2) The need for prolonged induction phase at the end of one month.
(3) Renal failure developing during treatment.
(4) Sepsis developing during one month
(5) Clinical improvement/ deterioration/discharge at 1 month
(6) The need of other therapies like ventilator care, antimicrobial treatment, etc.

Patients with or without COVID vaccination history were included.

RESULTS:

Demographic details:

The age distribution of the study population was as follows:

Table 1: Descriptive analysis of age groups in the study population (N=75)

Age group	Frequency	Percentage
<40	12	16%
41-50	23	30.7%
51-60	22	29.3%
61-70	13	17.3%
>70	5	6.7%
Total	75	100%

Majority of the patients were in the 40 to 60 years age group (60%). Only 6.7% of patients were older than 70 years. The mean age of diagnosis was 52 years with values ranging from 29 years to 83 years.

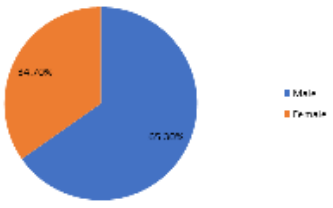

Figure 1: Pie chart of gender in study population (N=75)

Males were predominantly affected contributing 65.3% Details of the preceding COVID illness:

74.7% of patients had pulmonary symptoms during their COVID illness, 41.3% of patients had symptoms like fever, myalgia, 34.7% of patients had olfactory symptoms,

Table 2: Descriptive analysis of duration of hospital stay in days in study population

Duration of hospital stay in days	Frequency (N)	Percentage (%)
0	15	20%
1 -7	31	41.3%
8 - 10	13	17.3%
11-20	13	17.3%
>20	3	4%
Total	75	100%

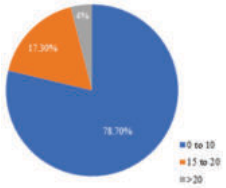

Figure 2: Pie chart of duration of hospital stay in days in study population (N=75)

Among the patients, 20% patients were in home quarantine. 78.6% of all patients had less than 10 days of hospital stay. The median duration of stay in the hospital was 7 days.

Table 3: Descriptive analysis of Duration of iv steroid in days in study population

Duration of iv steroid in days	Frequency (N)	Percentage (%)
0	16	25%
1-5	22	39%
6-10	19	25.3%
11-15	6	8%
16-20	2	2.7%
Total	75	100%

64% of the patients received 5 days of steroids or less. Only 2.7% of patients received more than 15 days of steroids. The patients received a median of 5 days of steroids.

Table 4: Descriptive analysis of type of oxygen support given in study population

Type of oxygen support given	Frequency (N)	Percentage (%)
Nasal oxygen	31	41.3%
CPAP NIV	2	2.6%
None	42	56.1%

Majority of the patients(56.1%) did not receive any form of oxygen support. Patients had a mean of 3.48 days of oxygen therapy during admission for COVID.

Details of admission during mucormycosis:

Table 5: Descriptive analysis of Type of mucormycosis in study population

Site of involvement	Frequency (N)	Percentage (%)
Rhino	22	29.3%
Rhino | Orbital	30	40%
Rhino | Orbital | Cerebral	23	30.7%

40% of the patients had rhino-orbital mucormycosis, followed by rhino-orbital-cerebral mucormycosis (30.7%) and rhino mucormycosis (29.3%).

Table 6: Descriptive analysis of clinical parameter in study population (N=75)

Parameter	Mean ± SD	Median	Min	Max
Admission CBG in mg/dl	242.7 ± 116.3	222	95	600
RBS in mg/dl	223.9 ± 115.7	203	65	658
FBS in mg/dl	200.9 ± 83.63	178	87	427
PPBS in mg/dl	253.7 ± 85.64	223	108	488
HbA1c in g/dl	11.14 ± 2.51	11.50	6	17
HCO3 in mEq/l	22.97 ± 1.69	23	20	26
Hb in g/dl	11.65 ± 1.97	11.40	7	17
TC in cells/mm3	10816 ± 4843	10900	17	22600
Platelet in lakhs/mm3	6.28 ± 24.24	3.20	1	213
Urea in mg/dl	29.03 ± 15.57	15.57	11	88
Creatinine in mg/dl	0.91 ± 0.53	0.80	0.5	3
Insulin total units per day	26.28 ± 23.2	24	0	85

The mean Fasting Blood Glucose and Post Prandial Blood Glucose were 178 mg/dl and 223 mg/dl respectively. The mean HbA1c was 11.5 g/dl.

Table 7: Descriptive analysis of Treatments given in study population

Treatments given	Frequency (N)	Percentage (%)
Medical management	75	100%
ENT procedure	67	89.3%
Orbital exenteration	6	8%

89.3% of patients needed ENT procedure and 8% needed orbital procedures (orbital exenteration or retrobulbar Amphotericin B).

Overall, 76% of patients had sepsis during hospital stay and 10.7% had developed acute kidney injury during hospital stay.

Table 8: Descriptive analysis of the clinical condition of the study population at the end of one month

Clinical condition at present	Frequency (N)	Percentage (%)
Still requires active treatment	17	22.7%
Discharged	55	73.3%
Death	3	4%
Total	75	100%

At the end of one month, 73.3% of patients were discharged, 22.7% of patients still needed active treatment at the end of one month, and 4% expired in the one month period.

Details of the glycemic profile of the patients during COVID illness and during mucormycosis:

57.3% of patients had h/o pre-existing diabetes. 61.3% of patients had hyperglycemia during COVID admission. Overall, 90.7% patients had hyperglycemia during mucormycosis treatment.The difference was statististically very significant (p value <0.001).

Table 9: Descriptive analysis of Euglycemia, Hyperglycemia and Severe hyperglycermia in study population

	Frequency	Percentage
Euglycemia (RBS or CBG <200 or HbA1c <6.5)	7	9.3%
Hyperglycemia (RBS or CBG>200 or HbA1c 6.5-10)	16	21.3%
Severe hyperglycermia (HbA1c >10 g/dl)	52	69.3%

Majority of the post COVID mucormycosis patients (69.3%) had severe hyperglycemia during the admission for mucormycosis. Six of the patients with severe hyperglycemia had diabetic keto acidosis (8% overall)

Table 10: Descriptive analysis of Euglycemia, Hyperglycemia and Severe hyperglycermia in study population among newly diagnosed diabetics and pre-existing diabetics:

	Frequency in non diabetics	Percentage	Frequency in previously diabetics	Percentage
Euglycemia (RBS or CBG <200 or HbA1c <6.5)	7	18.9%	0	0
Hyperglycemia (RBS or CBG>200 or HbA1c 6.5-10)	7	18.9%	9	20.5%
Severe hyperglycermia (HbA1c >10 g/dl)	17	54.8%	35	79.5%

23.25% of patients required insulin in the pre-existing diabetes group. 73.4% of patients required insulin during mucormycosis treatment, 54.6% of patients needed insulin treatment after discharge.

A median of 36 units of insulin per day were required during the hospital stay and 38 units of insulin per day were required post discharge.

Comparison of various outcome parameters among different classes of hyperglycemia:

There was no significant difference between euglycemic, hyperglycemic and severe hyperglycemic patients with respect to outcome (discharge, death and still requiring active treatment). There was no significant difference in outcome with regards to pre-existing diabetics and newly diagnosed diabetics.

The glycemic status of the patients during admission for mucormycosis did not have any significant association with the duration of oxygen support and the duration of iv steroids during COVID admission.There was also no significant difference between newly diagnosed diabetics and pre-existing diabetics. However, patients who needed some form of oxygen supplementation or those who needed iv steroids during COVID treatment also had hyperglycemia during admission for COVID. The observation was statistically significant (p value 0.003, 0.039 respectively).

Pre-existing diabetics had a statistically significant higher chance of developing sepsis (p value 0.047) and renal failure (p value 0.023) during mucormycosis admission than newly diagnosed diabetics.

DISCUSSION:

The median age at presentation was 52 years. The 40 to 60 years group was the most commonly involved age group (60%). Males were predominantly affected (65.3%). These findings correlate with the existing data of post COVID mucormycosis [4,6,7].

Considering the prior COVID illness, 80% of the patients were hospitalized, 20% were in home isolation. Among the hospitalized patients, 25% did not receive steroids, 39% received less than 5 days of steroids, 33.3% received steroids for 6 to 15 days, 2.7% received steroids for 16-20 days.The median steroid dosage was given for 5 days. The use of steroids was significantly higher among patients who had hyperglycemia during presentation of COVID illness. Whether hyperglycemia is a result of the glucocorticoid or whether hyperglycemia marked the severity of the underlying COVID, thus necessitating steroids could not be elucidated from our study because of the retrospective nature of the study. Though a vast majority of the study population has not received steroids or have received less than 5 days steroids, there was a very significant increase in the number of patients with hyperglycemia during admission for post COVID mucormycosis. This may suggest a minor role of steroids in causing post COVID diabetes. Existing literature also mentions the reversibility of steroid induced diabetes mellitus following withdrawal of the steroid[8]. Data is available on the mechanisms which cause diabetes post COVID including the role of ACE2 receptors in the pancreatic islet cells in insulin secretion, which is affected in COVID[4.9]. The mean Fasting Blood Glucose and Post Prandial Blood Glucose were 178 mg/dl and 223 mg/dl respectively probably indicating a deranged insulin secretion rather than a pure insulin resistance of steroids.

56.1% of the mucormycosis patients did not receive any form of oxygen supplementation during their COVID treatment, 41.3% received nasal oxygen and 2.6% needed CPAP. These percentages were different from existing reports[7], which show around 60% of patients had nasal oxygen. But, that study was on a smaller number of patients. Another small series[10] showed an even lower nasal oxygen received during COVID. The need for nasal oxygen was significantly higher among patients who had hyperglycemia during COVID treatment. This could reflect the increased severity of the COVID illness in hyperglemic patients. Strong evidence exists regarding the influence of cytokine storm in deciding the severity of COVID 19 infection. One review mentions that elevated ferritin in such severe inflammation in COVID can favour the growth of mucormycosis [4]. However, more studies are needed to prove this association between hyperglycemia, hyperferritinemia and mucormycosis.

The significant association between hyperglycemia during COVID treatment with steroid use during COVID treatment and nasal oxygen during COVID treatment may have implications on post COVID diabetes. Taken together, oxygen use and steroid use may predict hyperglycemia during COVID. All patients who had hyperglycemia during COVID treatment also had hyperglycemia during post COVID mucormycosis. 65.3% of the patients with hyperglycemia during COVID treatment were newly diagnosed. However, steroid use or nasal oxygen use did not have any statistically significant direct correlation with the glycemic status during admission for mucormycosis.

40% of the patients had rhino-orbital mucormycosis, followed by rhino-orbital-cerebral mucormycosis (30.7%) and rhino

mucormycosis (29.3%). This is in sharp contrast with the meta analysis conducted on post COVID mucormycosis[6], where rhinosinusitic mucormycosis was the commonest followed by rhino-orbital and then by rhino-cerebral mucormycosis.

57.3% of patients had pre-existing diabetes,61.3% had hyperglycemia during admission for COVID and 90.7% had diabetes during admission for mucormycosis. The difference was statististically very significant.

For analysis, our patients were classified into the following categories:(I) Patients with euglycemia (RBS or CBG <200 or HbA1c <6.5) on admission. (ii) Patients with hyperglycemia (RBS or CBG>200 or HbA1c 6.5-10) on admission. (iii) Patients with severe hyperglycermia (HbA1c >10 g/dl) on admission including patients with Diabetic Keto Acidosis (urine acetone positivity,) on admission We also wished to compare behaviour and outcomes between the following two distinct entities :. (i) Patients with history of diabetes mellitus prior to the diagnosis of COVID-19 infection (pre-existing diabetes mellitus) (ii) Patients with hyperglycemia diagnosed during or after COVID-19 infection. No other existing studies has compared these entities.

69.3% of patients had severe hyperglycemia during admission for mucormycosis, 21.3% had hyperglycemia and only 9.3% were euglycemic (91.7% had hyperglycemia overall, neglecting the severity). This correlates well with all reported literatute till now. Hence, hyperglycemia may be considered as the primary contributor to post COVID mucormycosis.

73.3% of patients were discharged by the end of one month. 22.7% of patients still continued to receive intensive phase therapy with Amphotericin B or iv posoconazole. Considering our institute protocol of minimum 3 weeks of induction phase regimen,for 73.3% of patients this was adequate. 22.7% of patients did not have adequate source control which warranted continuation of induction phase treatment at the end of one month. 4% was the mortality in this study. This is far less than existing lliterature[5], which reports a mortality of upto 30.2%. There was no significant difference in these outcomes among patients with euglycemia, hyperglycemia or with severe hyperglycemia. There was also no significant differences in outcome between pre-existing diabetics and newly diagnosed diabetics during or post COVID.

23.25% of patients required insulin in the pre-existing diabetes group. 73.4% of patients required insulin during mucormycosis treatment, 54.6% of patients needed insulin treatment after discharge.

Overall, 76% of patients had sepsis during hospital stay and 10.7% had developed acute kidney injury during hospital stay. The Acute Kidney Injury could be due to the effect of Amphotericin B or secondary sepsis. Pre-existing diabetics had a statistically significant higher chance of developing sepsis and renal failure than newly diagnosed diabetics.

CONCLUSION:

Four important conclusions were drawn from our study:

(I) Shorter duration of steroid intake and shorter duration of supplemental oxygen makes a direct role of steroids or contaminated oxygen less likely to be a cause of Covid Associated Mucormycosis.

(ii) Higher steroid use and higher oxygen requirement were associated with hyperglycemia in both pre-existing diabetes and in non-diabetics. This could indicate the underlying severity of COVID illness and its correlation with hyperglycemia.

(iii) There was a significantly higher incidence of hyperglycemia during mucormycosis than in the preceding COVID illness again pointing towards a hyperglycemic effect of COVID as such.

(iv) Only in-hospital sepsis and renal failure were significantly higher among pre-existing diabetics than newly diagnosed diabetics. Otherwise, there was no other difference in outcomes among various grades of severity of hyperglycemia during mucormycosis or between pre-existing diabetics and newly diagnosed diabetics during or post COVID.

The knowledge about the pathogenesis of post COVID hyperglycemia and mucormycosis is essential to prevent future outbreaks of mucormycosis.

Relevance of the study, limitations and future prospects:

Very few studies exist regarding mucormycosis due to its rarity. COVID Associated Mucormycosis has resulted in a surge of this rare disease leading to a scope of research into clarity. This study is one of the large series available till date. Hence, results from this study may help in framing hypothesis regarding the new disease of COVID Associated Mucormycosis.

This study has few limitations like lack of data on COVID vaccination status. More studies are needed to prove or refute existing data.

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