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PREDICTORS OF MORTALITY IN PATIENTS WITH CONCOMITANT AND SEQUENTIAL COVID -19 ASSOCIATED MUCORMYCOSIS - A CROSS SECTIONAL STUDY IN A TERTIARY CARE CENTER.

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Abstract:
Introduction: Mortality rates for COVID-19-related mucormycosis vary greatly in reported studies. A systematic evaluation of 101 cases revealed a fatality rate of 30.7 percent. However, research on the determinants of death in COVID-19 associated mucormycosis is insufficient. The purpose of this study was to find out what factors contributed to in-hospital mortality in patients with COVID-19-related mucormycosis.
Objectives:
To study the the Clinical profile , Haematological ,Biochemical and Radiological changes associated with mortality in patients with covid-19 associated mucormycosis.
Methodology: In this single-center, observational study, 130 patients diagnosed with COVID-19 associated mucormycosis were recruited from a tertiary level intensive care unit from Bowring and Lady Curzon hospital, Bangalore, India.
Results: Proportion of HTN, IHD, CKD and HIV was significantly more in non survivors compared to survivors. ICU admission and Oxygen requirement was scientifically higher in Non Survivors and had significant association with the outcome. . There was no significant difference in the levels of Hb, Neutrophils, Lymphocytes, Monocytes, Eosinophils, and Platelets as $p>0.05$. Total count (17191±7764), ESR (57.6±12.4), CRP levels (199.0±69.5), and S.Ferritin (624.6±268.0) were significantly higher among the Non survivors. S.LDH (355.7±108.9), S.Free Iron (51.7±13.3), HBA1C (11.4±2.4), and S.Urea (36.9±35.3) were also found to be significantly higher among the non survivors.
Conclusion: The current study highlights that a multidisciplinary approach in COVID-19 associated mucormycosis patients that includes timely and effective surgical debridement coupled with appropriate antifungal therapy and diligent sugar monitoring with intrahospital glycemic control may help to lower mortality.

Introduction

The world has been seeing the deadly coronavirus disease 2019 (COVID-19) pandemic for the last two years, which has caused enormous morbidity and mortality [1]. Though the majority of COVID-19 patients have mild to moderate disease, a number of risk factors, including age and comorbidities (e.g., obesity, cancer, diabetes), predispose persons to severe disease [2,3]. The optimum treatment for COVID-19 is currently unknown, and management varies depending on the severity of the disorder. However, the administration of steroids in hospitalised patients was associated with a reduction in mortality [4]. During the second wave of the COVID-19 pandemic, India had a considerable increase in the incidence of COVID-19 associated Mucormycosis, accounting for more than 70% of all COVID-19 associated Mucormycosis cases globally [5]. The global prevalence of Mucormycosis in the

general population ranges from 0.005 to 1.7 per million people. India, on the other hand, has an 80-fold higher frequency of mucormycosis than developed countries [6]. COVID-19-associated mucormycosis is seen in individuals who are on COVID-19 or who are in convalescence. Uncontrolled diabetes, respiratory disorders including viral/bacterial infections, cancer (e.g., haematological), and the immunocompromised state are all risk factors for COVID-19 linked mucormycosis [7,8].

In documented investigations with COVID-19 related mucormycosis, mortality rates vary significantly [7,9]. A 30.7 percent death rate was found in a comprehensive review of 101 cases [8]. However, research on the predictors of death in COVID-19 linked mucormycosis is inadequate. The goal of this study was to identify determinants of in-hospital mortality in patients with COVID-19 related mucormycosis.

OBJECTIVES:
To study the the Clinical profile , Haematological ,Biochemical and Radiological changes associated with mortality in patients with covid-19 associated mucormycosis .

Materials And Methods
In this single-center, observational study, patients diagnosed with COVID-19 associated mucormycosiswere recruited from a tertiary level intensive care unit from Bangalore, India. Equipped with modern facilities, our ICU provides the tertiary level of intensive care to urban and semi-urban populations. The study was conducted according to the principles of the Declaration of Helsinki and good clinical practice, and local applicable regulatory guidelines. The institutional ethics committee (biomedical and health research) of Bowring and Lady Curzon hospital(institutional review board) approved the study. The consent was waived as this was a retrospective study. The study was conducted between May 2021 to August 2021.

E. Inclusion Criteria :
1. Age >18 years
2. All patients who succumbed due to concomitant or sequential COVID-19 associated mucormycosis

F. Exclusion Criteria:
1. Patients with other serious comorbid conditions including CKD, Malignancies, IHD

Data from the case record proforma were entered into Microsoft Excel spreadsheet version 2016 and analyzed using IBM-SPSS version 24. Frequency and proportion (percentages) expressed the categorical data. The normality of continuous data was decided by plotting histograms. Normally distributed continuous variables were expressed as mean and SD (standard deviation). For determining the statistical differences in categorical data, a Chi-square test was applied. For normally distributed continuous data, a student t-test was applied, whereas, for non-normal continuous data, the non-parametric test of Mann-Whitney U was applied. Multinomial logistic regression analysis was done to identify the predictors of mortality. P-value < 0.05 was considered significant for all statistical comparisons.

Results
In total, 130 patients identified to have COVID-19 associated mucormycosis were included in the analysis.Out of 130 subjects, 50 were survivors and 80 were non suvivors. Baseline characteristics along with details of COVID-19 are presented in Table 1.Of the 130 patients,26.15% were Concomitant and 73.85% were sequential. The mean age was 49 ± 12

years, and 75.3% were males. Diabetes mellitus (96.15%) and hypertension (48.4%) were the major comorbid conditions. Only 1.5% subjects received COVID-19 vaccinations. Proportion of HTN, IHD, CKD and HIV was significantly more in non survivors compared to survivors. ICU admission and Oxygen requirement was scientifically higher in Non Survivors and had significant association with the outcome.

Table 1: Baseline charaterstics

		Survivor		Non Survivor		
		N	%	N	%	p-value
SEX	Female	10	20.0%	22	27.5%	0.000
	Male	40	80.0%	58	72.5%	
STAGING	1	39	78.0%	0	0.0%	0.000
	2	11	22.0%	20	25.0%	
	3	0	0.0%	60	75.0%	
CONCOMITANT / SEQUENTIAL	Concomitant	8	16.0%	26	32.5%	0.000
	Sequential	42	84.0%	54	67.5%	
DM	No	1	2.0%	4	5.0%	0.000
	Yes	49	98.0%	76	95.0%	
HTN	No	36	72.0%	31	38.8%	0.000
	Yes	14	28.0%	49	61.3%	
IHD	No	43	86.0%	51	63.8%	0.000
	Yes	7	14.0%	29	36.3%	
CKD	No	48	96.0%	74	92.5%	0.000
	Yes	2	4.0%	6	7.5%	
CHEMO/RADIO	No	49	98.0%	80	100.0%	0.000
	Yes	1	2.0%	0	0.0%	
HIV	No	50	100.0%	79	98.8%	0.000
	Yes	0	0.0%	1	1.3%	
SURGERY	No	22	44.0%	42	52.5%	0.000
	Yes	28	56.0%	38	47.5%	
ICU admission	No	37	74.0%	31	38.8%	0.000
	Yes	13	26.0%	49	61.3%	
O3	No	0	0.0%	31	38.8%	0.000
	Yes	50	100.0%	49	61.3%	
STEROID	No	0	0.0%	45	56.3%	0.000
	Yes	50	100.0%	35	43.8%	
Covid Vaccination	No	50	100.0%	78	97.5%	0.000
	Yes	0	0.0%	2	2.5%	
HIV	Negative	50	1	80	1	0.000
HBsAg	Negative	50	1	80	1	0.000
HCV	Negative	50	1	80	1	0.000
INJ AMPHO	No	0	0	18	0.225	0.000
	Yes	50	1	62	0.775	
INJ POSA	No	0	0	45	0.5625	0.000
	Yes	50	1	35	0.4375	

Details of mucormycosis in study patients are shown in Table 2.
The mean age of the Non survivors was significantly higher (57±13 years) compared to survivors (49±12 years), $p<0.05$. There was no significant difference in the levels of Hb, Neutrophils, Lymphocytes, Monocytes, Eosinophils, and Platelets as $p>0.05$. Total count (17191±7764), ESR (57.6±12.4), CRP levels (199.0±69.5), and S.Ferritin (624.6±268.0) were significantly higher among the Non survivors.
S.LDH (355.7±108.9), S.Free Iron (51.7±13.3), HBA1C (11.4±2.4), and S.Urea (36.9±35.3) were also found to be significantly higher among the non survivors.
Mean Na+ was found to significantly lower (133.0±5.0) among the non survivors, compared to the survivors.
There was no significant in mean S.Creatinine, Cl-, K+, TB, ALT, AST, and ALP, between the two groups.

Table2: Clinical characteristics.

	Survivor		Non Survivor		
	Mean	SD	Mean	SD	p-value
AGE	49	12	57	13	0.021
Hb	11.3	1.5	11.9	2.2	0.102
TC	10529	4126	17191	7764	0.000
N (Neutrophils)	73.1	12.6	74.5	9.3	0.458
L (Lymphocytes)	16.6	9.8	17.1	9.1	0.768
M (Monocytes)	7.18	3.61	7.26	2.93	0.901
B (Basophils)	0.72	0.93	1.25	1.16	0.008
E (Eosinophils)	2.1	2.3	1.7	1.7	0.354
Platelets	3.4	1.2	6.5	32.8	0.506
ESR	39.6	15.4	57.6	12.4	0.000
CRP	70.8	42.3	199.0	69.5	0.000
D-Dimer	506.9	226.2	650.2	255.1	0.002
S.Ferritin	321.1	57.0	624.6	268.0	0.000
S.LDH	220.4	90.9	355.7	108.9	0.000
S.Free Iron	34.2	5.2	51.7	13.3	0.000
HBA1C	8.6	1.6	11.4	2.4	0.000
S.Urea	25.0	19.6	36.9	35.3	0.031
S.Creatinine	3.0	13.9	1.1	1.2	0.244
Na+	135.4	5.1	133.0	5.0	0.009
Cl-	93.9	23.3	97.9	12.4	0.204
K+	7.8	18.7	5.0	10.9	0.291
TB	0.3	0.7	1.3	5.9	0.201
ALT	32.7	26.3	40.1	37.3	0.221
AST	22.1	13.8	23.4	26.8	0.749
ALP	98.8	66.3	103.5	88.3	0.751
TP	5.6	1.0	10.0	6.8	0.000
ALBUMIN	3.0	0.5	2.0	0.5	0.000
PT/INR/aPTT	13.9	1.9	14.6	2.1	0.075
INR	1.1	0.2	1.2	0.1	0.048
APTT	30.5	9.1	33.9	7.1	0.022

Discussion

Mucormycosis has posed a dangerous threat in India during the second wave of the COVID-19 pandemic. India contributed nearly three-fourth of the total burden of mucormycosis globally. It is probably because of the substantial presence of undiagnosed as well as uncontrolled diabetes in India [12]. Mucormycosis has variable presentations. The rhino-cerebro-orbital mucormycosis is the major form observed in this pandemic. Diagnosis is established through CT paranasal sinus and MRI brain [13]. After assessing 101published cases of mucormycosis, Singh et al. observed that involvement of nose and sinuses (88.9%) was most common, followed by rhino-orbital (56.7%) [8]. Rhino-orbital disease can progress to CNS involvement which was observed in 28.1% of patients. Rhino-orbital-cerebral mucormycosis is a serious, severe, emergent, and fatal infection associated with high mortality. During the study period a total of 520 subjects with Mucormycosis were admitted in the hospital, out of which 80 patients died. The mortality rate in this study was 15.3%. It is much lower to reported rates of 64.3% from Singh et al. [7], 47% from Pakdel et al. [9], 40% from Sarkar et al. [14], and 30.7% from Singh et al. [8]. Even in patients without COVID-19, Jiang and colleagues reported survival of only three out of 11 patients who had invasive rhino-orbital-cerebral mucormycosis [15]. Our findings suggest that lower mortality in our study is due to the implementation of protocolized management of COVID-19 related mucormycosis, which includes timely and effective surgical debridement, appropriate antifungal therapy, diligent blood sugar monitoring, and good intrahospital glycemic control in the context of multidisciplinary medical care.It is necessary to diagnose early and initiate treatment. A delay of six days in starting the treatment increases the 30-day mortality risk by two-fold from 30% to 60% [16].

Deutsch et al. reported that the intracranial involvement of mucormycosis increases the fatality rate to as high as 90% [17]. COVID-19 itself has a high likelihood of developing mucormycosis. The presence of hypoxia, hyperglycemia, high ferritin levels, and reduced phagocytic activity of leucocytes can contribute to the development of COVID-19 associated mucormycosis [8]. In patients with COVID-19, CKD incidence is higher (4.09%) compared to the general population (0.46%). The presence of CKD increases mortality significantly (44.6% compared to 4.7% in those without COVID-19) [18]. This was also clear from our observation that mortality is increased in COVID-19 associated mucormycosispatients who develop AKI. The use of tocilizumab carries the risk of infections late in the course of the disease. Pettit et al. reported infectious complications in 23% of patients after 48 hours of admission; there were three cases of invasive fungal infections in a total of 74 patients [19].

Among the risk factors, diabetes mellitus, especially uncontrolled diabetes, is a significant risk factor for mucormycosis [20]. Though diabetes was seen in 70.2% of patients, we found no association of diabetes with mortality. Though uncontrolled blood sugar levels are one of the risk factors for COVID-19 associated mucormycosis, average HbA1c did not differ significantly in survivors and non-survivors. The impact of diabetes on mortality in patients with COVID-19 associated mucormycosisneeds further evaluation in a more extensive study. In addition to these factors, old age is also a factor detrimental to the outcome of COVID-19 associated mucormycosis.

Fungal infections are frequent in uncontrolled Diabetes patients, according to Chakrabarti A, Das A.etal. [21]

According to JHU etal, COVID-19-associated mucormycosis (COVID–Mucor), manifesting as rhino-orbito-cerebral mucormycosis (ROCM), has increased morbidity in vulnerable populations. Infection with SARS-CoV-2, high blood sugar, corticosteroids, and iron excess

all produce phagocyte dysfunction, which is likely the more immediate cause of mucormycosis. [22]

According to Lammaert et al., 2012, mean serum ferritin levels, a hallmark of immunological dysregulation and an essential component of iron metabolism, were significantly higher among cases. SARS-CoV-2 infection, together with probable changes in iron metabolism, may have predisposed to mucormycosis in addition to hyperglycemia and steroid use. [23]

Montefusco,Ben Nasr M et al., [24] 2021 reported hyperglycemia persisting up to 3 months related with COVID-19. Steroid usage appears to cause hyperglycemia due to an abnormal cytokine milieu and insulin resistance, rather than beta cell infection, and steroid use was substantially linked with mucormycosis (OR 28.4; P = 0.001). Despite widespread use in rheumatological illnesses, the frequency of mucormycosis remains low, implying that steroid use, along with other causes, is to blame for the COVID–Mucor epidemic in India.

According to Patel et al., Agarwal R,(2021), the vast majority of patients, 97 percent, had underlying diabetes mellitus in their study, a rate higher than that found in an Indian multicenter COVID–Mucor study conducted during the first wave of the COVID-19 pandemic, in which two-thirds of patients had this disease. [25]

Our study was limited by retrospective design, single-center, and small sample. Though the in-hospital mortality rate was lower than most reported studies, the lower event rate makes it difficult to draw substantial conclusions for the predictors of mortality. Nonetheless, the study identified that orbital involvement and renal dysfunction to be associated with high mortality.

Conclusions

Mucormycosis in patients with COVID-19 is a double-trouble that causes significant morbidity and morbidity. The rise in COVID-19 associated mucormycosisin India posed a substantial threat as a higher number of cases were detrimental to the health of the individuals and community. The current study highlights that a multidisciplinary approach in COVID-19 associated mucormycosispatients that includes timely and effective surgical debridement coupled with appropriate antifungal therapy and diligent sugar monitoring with intrahospital glycemic control may help to lower mortality. We suggest ophthalmic and brain screening early in the course of COVID-19 associated mucormycosispatients to improve survival. In addition, comorbidities such as CKD and renal dysfunction can contribute to increased mortality. Control of risk factors such as diabetes, judicious use of immunomodulators to avoid immunosuppression along with early diagnosis and treatment is the key to improving survival in mucormycosis patients with COVID-19.

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