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Original Research Article

Study on serum iron profile in COVID-19 associated mucormycosis patients

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ABSTRACT

Background: Mucormycosis is an angio-invasive disease caused by fungi prevalence of which in India is approximately 0.14 cases per 1000 population. The incidence of mucor in COVID 19 patients has increased to greater extent. Probable cause of which is increased serum ferritin among these patients and Iron is required by virtually all microbial pathogens for growth and virulence. Hence, we had conducted a study to estimate serum iron profile and association of iron profile with mucor mycosis in covid-19 associated mucormycosis.
Methods: Cross sectional study conducted from May 2021 to July 2021 by the department of general medicine, Banglore medical college and research centre, Karnataka. The data collected was analyzed statistically using descriptive statistics.
Results: We observed increased prevalence of mucor cases among the patients aged between 41 to 60 years and those who were not vaccinated. Hyperglycaemia had strong correlation with development of mucor. There was lower UIBC, lower TIBC, high ferritin and serum Iron levels among those who had developed mucormycosis.
Conclusions: By our observations, we concluded that the increased serum iron, ferritin, transferrin and reduced TIBC and UIBC are the associated risk factor in the development of COVID 19 associated invasive mucor mycosis. Patients with HbA1c >7 are at higher risk of developing COVID 19 associated mucor mycosis.

Keywords: COVID 19, Mucormycosis, Serum iron profile, UIBC, TIBC, Ferritin

INTRODUCTION

On 31st of December in the year 2019, WHO was informed about the pneumonia cases of unknown etiology detected in Wuhan city, China. Later in January novel corona virus (SARS-CoV-2) was isolated from pneumonia patients, and the disease was referred as COVID 19. WHO declared COVID 19 outbreak as pandemic in march 2020.[1] The clinical spectrum of SARS-CoV-2 infection is wide, ranging from asymptomatic infection, mild upper respiratory tract infection, moderate and severe viral pneumonia with respiratory failure and may lead to death with many requiring hospital care.[2] Though initially thought to be zoonotic disease there is considerable human to human transmission of the virus with considerable infectivity rate.[3]

The first reported case in India was on 30th January 2020, index case being a Wuhan return student. The first wave of COVID 19 in India began in the month of march with the surge of cases towards end of April 2020. The spread of the COVID 19 was a challenge for the medical fraternity with the fact that little was known about the disease with rapid surge in the cases. Potential risk factors for disease severity were found to be elderly, patients with co morbidities, higher D dimer levels and high qSOFA score.[2,4] With the help of multiple clinical

trials, management protocols, preventive measures of viral transmission COVID 19 was managed.

The second wave of COVID 19 began in India in the month of February 2021 with a surge of cases, 3447133 cases as of on 4th May 2021.[5] The scenario in second wave is much worse than the first wave as the spread is much faster with exponential increase in the number of cases and the steeper curve, though the case fatality rate is found to be improved.[6] It is observed that more younger patients being affected and more number of patients requiring hospital care with oxygen dependency and disease severity.[7]

Mucormycosis is an angioinvasive disease caused by fungi of the order Mucorales like Rhizopus, Mucor, Rhizomucor, Cunninghamella and Absidia.[8] The prevalence of mucormycosis in India is approximately 0.14 cases per 1000 population, about 80 times the prevalence in developed countries. Given the increasing prevalence of diabetes, cancer, and organ transplantation in the aging United States population, the rise in incidence of mucormycosis is anticipated to continue unabated for the foreseeable future.[9]

Iron is required by virtually all microbial pathogens for growth and virulence. In mammalian hosts, very little serum iron is available to microorganisms because it is highly bound to carrier proteins such as transferrin.[10]

Importantly, patients with elevated levels of available serum iron are uniquely susceptible to infection by R. oryzae and other Zygomycet.[11]

Patients with diabetic ketoacidosis have elevated levels of available serum iron, likely due to release of iron from binding proteins in the presence of acidosis.

Objectives of the study

To estimate serum iron profile in covid-19 associated mucormycosis patients. To correlate serum iron profile with clinical severity of mucormycosis.

METHODS

Source of data

COVID19 patients getting admitted in hospitals attached to BMCRI.

Methods of collection of data

Cross sectional study conducted from May 2021 to July 2021 by the department of general medicine, Banglore medical college and research centre, Karnataka.

Sample size

Based on the severity of pandemic.

Inclusion criteria

Patients or attenders willing to give informed consent for study. Age >18 years. Clinically and microbiologically or radiologically confirmed cases of COVID 19 pneumonia requiring hospital admission. Clinically and microbiologically or radiologically confirmed cases of mucormycosis

Exclusion criteria

Patients with loss to follow up in case of discharge against medical advice and transfer to other hospitals.

Methodology

After obtaining Institutional ethical committee clearance, cases were selected as per the inclusion criteria mentioned above and written informed consent was taken. Relevant blood investigations will be sent.

Statistical analysis

The data collected was analyzed statistically using descriptive statistics namely mean, standard deviation, percentage wherever applicable. Appropriate parametric and non-parametric tests was used.

RESULTS

The study was conducted from May 2021 to July 2021, during the second wave of COVID-19 pandemic in Bengaluru. Patients diagnosed with COVID-associated Mucormycosis in hospitals attached to BMCRI were included. We analysed 110 patients of COVID-associated Mucormycosis with respect to their characteristics, co-morbidities, iron status among other factors.

Table 1: Distribution of age.

Age in years	N	%
21 to 40	19	17.3%
41 to 60	71	64.5%
61 to 80	18	16.4%
>80	02	1.8%

Based on the analysis, the most common age group affected with COVID-associated Mucormycosis was between 41 to 60 years of age accounting for about 64.5% of the study population.

There was significantly higher prevalence of mucor among males accounted for about 77 (70%) males and 33 (30%) females with $p<0.05$ which is illustrated in figure 2.

Out of 110 patients, 85 patients (77.3%) were suffering from Diabetes Mellitus followed by 29 (26.4%) patients with hypertension. We observed significant number of

patients with comorbid conditions than those without any previous history of comorbid conditions. Which is also illustrated in figure 2.

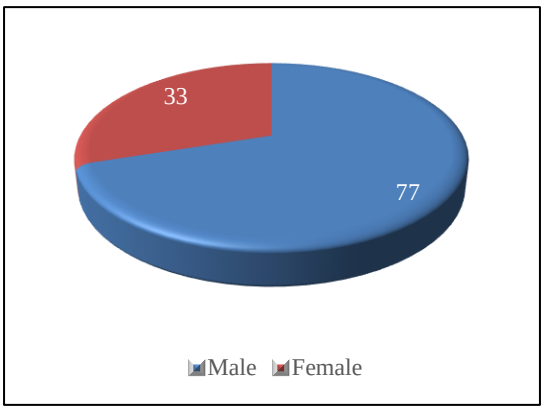

Figure 1: Distribution of gender.

Table 2: Distribution of history of comorbid conditions.

Comorbid condition	N	%
Hypertension	29	26.4%
Diabetes	85	77.3%
IHD	05	4.5%
CVD, CVA	02	1.8%
HbsAg positive	02	1.8%
Nil	25	22.7%

p<0.05

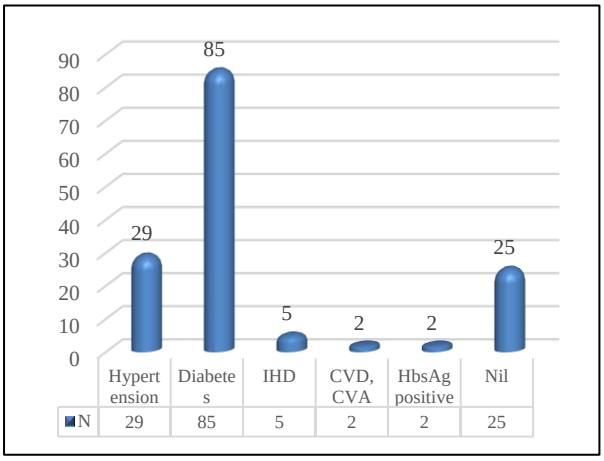

Figure 2: Distribution of comorbid conditions.

Majority of the patients developed mucor were not vaccinated but there was no statistically significant difference observed.

Distribution of the extension of mucor observed on CT was widely distributed.

Chronic hyperglycaemia as defined by HbA1c >6.5 which was significantly associated with the mucor mycosis among the recruited study population accounting for about 92 (83.6%) of the study population with p<0.05.

Table 3: Vaccination status.

Vaccinated	N	%
Yes	42	38.2%
No	68	61.8%

Table 4: Extension of mucor mycosis as observed on CT.

Extension	N	%
Pansinusitis with inflammation in right periantral region and infratemporal fossa and suspicious erosion in right maxillary sinus	18	16.4%
B/L frontal, ethmoidal, infratemporal involvement	14	12.7%
Invasive rhinosinusitis with orbital cellulitis	06	5.5%
Left transverse and sigmoid sinus involvement	01	0.9%
Invasive rhinosinusitis with Left/inferior cerebral subacute infract	11	10.0%
Unilateral ethmoidal sinus involvement	21	19.1%
Maxillary sinus involvement	19	17.3%
Frontal sinus involvement	07	6.4%
Sphenoid	10	9.1%
Orbital involvement	3	2.7%

Table 5: Distribution of HbA1c.

HbA1C	N	%
<6.5	18	16.4%
>6.5	92	83.6%

p <0.05

Table 6: Distribution of iron profile.

Parameter normal range	N	N	%	P value
Serum Iron (46 to 132mcg/dl)	<46	02	1.8%	0.0001
	50 to 132	26	23.6%	
	>132	82	74.5%	
Serum ferritin (12 to 270 mcg/dl)	<12	01	0.9%	0.0001
	12-270	25	22.7%	

Continued.

Parameter normal range	N	N	%	P value
	>270	84	76.4%	
TIBC (246-474 mg/dl)	246	84	76.4%	0.001
	246 to 474	25	22.7%	
	>474	01	0.9%	
Transferrin saturation (0.12 to 0.46)	0.12	01	0.9%	0.001
	0.12-0.46	29	26.4%	
	>0.46	81	73.6%	
UIBC (110 to 343 mcg/dl)	<110	88	80.0%	<0.05
	110-343	21	19.1%	
	>343	01	0.9%	

Table 7: Distribution of iron profile among DM patients.

DM		N	Mean	Std. deviation	P value
SIRON	Yes	83	39.771	9.6911	0.037
	No	25	40.960	12.1672	
UIBC	Yes	83	72.193	16.1940	0.05
	No	25	94.280	14.2583	
TIBC	Yes	83	204.000	17.8218	0.58
	No	25	210.280	15.7215	
TSAT	Yes	83	29.566	29.3857	0.03
	No	25	37.680	47.5445	
Transferrin	Yes	83	81.143	19.0931	0.05
	No	25	73.240	19.3420	
Ferritin	Yes	83	921.5771	20.74718	0.49
	No	25	905.023	56.19595	
HB	Yes	71	13.4715	10.09883	0.935
	No	22	13.6500	1.43916	
TC	Yes	71	545.446	2692.6129	0.178
	No	22	1562.927	4081.7493	
Neutrophils	Yes	15	83.267	8.0220	0.573
	No	8	81.375	6.4794	
Lymphocyte	Yes	15	11.9140	7.31931	0.943
	No	8	12.1250	5.19443	

Table 8: Distribution average values of laboratory parameters versus the HbA1c levels.

		N	Mean	Std. deviation	P value
SIRON	<6.5	18	35.6	15.489	0.043
	6.5-7.5	6	39.0	9.716	
	>7.5	86	43.0	19.394	
UIBC	<6.5	18	76.9	33.819	0.960
	6.5-7.5	6	79.7	12.355	
	>7.5	86	85.1	15.967	
TIBC	<6.5	18	204.0	67.250	0.837
	6.5-7.5	6	216.7	22.545	
	>7.5	86	118.6	76.212	
TSAT	<6.5	18	28.7	28.617	0.914
	6.5-7.5	6	34.7	42.453	
	>7.5	86	31.8	34.885	
Transferrin	<6.5	18	69.3	64.956	0.170
	6.5-7.5	6	87.0	73.189	

Continued.

		N	Mean	Std. deviation	P value
	>7.5	86	89.53	06.862	
Ferritin	<6.5	18	865.9	546.893	0.784
	6.5-7.5	6	696.6	647.669	
	>7.5	86	849.3	528.644	
HB	<6.5	16	12.4	1.993	0.839
	6.5-7.5	4	13.2	2.533	
	>7.5	75	13.8	9.781	
TC	<6.5	16	14.9	4.757	0.162
	6.5-7.5	4	3258.9	6494.068	
	>7.5	75	798.3	3109.368	
Neutrophils	<6.5	3	79.3	15.948	0.533
	6.5-7.5	3	86.3	6.658	
	>7.5	17	82.5	5.821	
Lymphocyte	<6.5	3	12.7	11.590	0.859
	6.5-7.5	3	10.0	8.718	
	>7.5	17	12.2	5.614	

Table 6 illustrated the distribution of iron profile among the recruited samples. Which shows that the number of patients with significantly high ferritin, TIBC, serum iron and significantly lesser UIBC were more than those with normal profile. As these parameters indicates the increased severity of the COVID 19, indirectly indicates here that the patients with significantly higher ferritin, iron, TIBC and reduced UIBC.

We observed that the average serum ferritin, S. iron and transferrin saturation were significantly higher among those presented with previous history of DM than without DM whereas TIBC and UIBC significantly lower.

DISCUSSION

In this cross-sectional study, involving Covid-associated Mucormycosis, most of the patients had Diabetes Mellitus with Chronic Hyperglycemia, with an iron overload state defined by elevated serum iron and serum ferritin levels, with a low TIBC and UIBC levels.

We observed higher prevalence of mucor cases among male patients and those who are aged between 41 to 60 years. 61.8% of the recruited study population were not vaccinated. Though there was increased severity among those who were not vaccinated, there was no statistically significant difference observed. This finding is in consistent with the study by Kumar et al in which the prevalence of diabetes mellitus among cases and controls was 75% versus 42.3% with p 0.015.[12] Diabetes confers an increased risk of Mucormycosis in patient affected with COVID-19. In our study 76% of the study population, were Diabetic.There was a high prevalence of Chronic Hyperglycemia as defined by HbA1C >6.5, seen in 92 (83.6%) patients affected with Covid-associated Mucormycosis in this study. We had observed the significantly higher average value of ferritin, TIBC and serum iron levels among diabetic patients but as the prevalence of DM among the recruited samples was itself higher the association cannot be specific. Bhanuprasad et al in their study also observed significantly higher number of patients with >6.5 HbA1c had developed invasive mucor mycosis.[13] This is also in consistence with the report by Patel et al and Montefusco et al.[14,15]

Iron overload state is associated with a lower UIBC, lower TIBC, high ferritin and serum Iron levels. The patients with higher HbA1c also has showed the similar distribution of iron profile. (Table 7, 8) In our study a low TIBC and UIBC levels was significantly associated with CAM especially in the age group of 40-60 years. Currently, iron profiling is not routinely done in COVID-19 affected patients, our findings of the additional risk of iron overload state, provide initial support for risk stratification for CAM. Our observations were in considtent with the findings by Kumar et al observed higher TIBC among their case group which is similar to Karp et al.[12,16] Abe et al observed lower UIBC among the patients with diabetes associated fungal infection.[17] They stated that the decreased serum UIBC produced by diabetic ketoacidosis enhances the growth of R. oryzae in vivo. Which can be correlated with our findings as we had higher prevalence of patients with HbA1c >6.5 and majority with uncontrolled DM.

We examined a range of iron parameters, co-morbidities in a small population of patients. Our study certain methodologic limitation, as it is a cross sectional study, we could not show causality between iron overload state and CAM and we could not compare the iron profile between mucor COVID associated mucor versus non mucor cases, which could have been given the reference range and cut off values for the risk of mucor cases.

CONCLUSION

Increased serum iron, ferritin, transferrin and reduced TIBC and UIBC are the associated risk factor in the

development of COVID 19 associated invasive mucor mycosis. The patients with HbA1c >7 are at higher risk of developing COVID 19 associated mucor mycosis. Patients who are not vaccinated against COVID 19 are at risk of developing CAM.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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