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Original Research Article

Estimation of triple prognostic factors: serum ferritin, D-dimer and HbA1c levels in post-COVID mucormycosis patients: a cross-sectional observational study

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ABSTRACT

Background: India was furiously hit by the second wave of COVID-19 that peaked during the months of April and May 2021. It led to an unprecedented number of rhino-orbital-cerebral mucormycosis cases that came as a bitter surprise. Several parameters were found to be consistently elevated in the patients like serum ferritin, D-dimer, and HbA1C.
Methods: A cross-sectional observational study was conducted at the SMS medical college that included 120 patients presenting with post-COVID mucormycosis from 1st May to 31st May 2021. HbA1c, D-dimer, serum ferritin levels were measured at the time of admission.
Results: Our study showed a mean range of serum ferritin of 539.6±484.9, mean D-dimer range was 636.3±303.5, both of which were higher than normal. In the present study 94.1% of the patients had diabetes mellitus. Among them 60.80% of the patients had newly detected diabetes and 33.30% were known cases of diabetes with mean HbA1c 9.7±2.3. The p value was less than 0.001 which was statistically significant.
Conclusions: Timely detection and categorization of the patients based on severity of the above parameters can not only help in executing the existing institutional resources but can also help in saving valuable lives, and preventing radical surgical procedures like orbital exenteration and maxillectomy.

Keywords: COVID-19, Mucormycosis, Serum ferritin, D-Dimer, HbA1c

INTRODUCTION

India was hit strongly by mucormycosis during the second wave of the COVID-19 pandemic. Mucormycosis is an invasive fungal infection caused by a group of environmental saprophytes-Rhizpous, Aposphysomyces, Licitheimia (Absidia), Saksenaea, Cunninghamella.[1] Novel severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) resulted in approximately 645 million cases and 6.6 million deaths worldwide while in India there were approximately 44 million confirmed cases and 0.5 million deaths.[2] An increasing number of studies are focusing on risk factors of mucormycosis. Commonly identifiable risk factors for mucormycosis are diabetes mellitus, patients receiving immunosuppressive therapy, leukaemia, neutropenia, neutrophil dysfunction, hematopoietic stem cell transplantation, diabetic ketoacidosis, iron overload and human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome (AIDS).[3] Studies have shown that early diagnosis and timely initiation of drug therapy are key factors in reducing mortality from mucormycosis. Previous studies have shown significantly elevated levels of D-dimer in patients infected with COVID-19. Elevated levels of D-

dimer indicate increased clotting leading to thrombus formation, which is the focus of fungal infections, and elevated serum ferritin also indicates immune system dysregulation in severe COVID infection. Few studies have compared levels of these important mediators-serum ferritin and D-dimer in COVID-19 patients with mucormycosis.[4-6] Therefore, this study aimed to assess potential risk factors in COVID-19 infected patients who develop mucormycosis.

METHODS

The present study is a cross-sectional observational study conducted at the SMS medical college and hospital, Jaipur from 1st May to 31st May 2021. 120 patients with confirm post-COVID Mucormycosis were included in the study. HbA1c, D-dimer, serum ferritin levels were measured at the time of admission. Patients with no prior history of COVID were excluded from the study. Adequate medical history and preoperative examination and laboratory tests were performed as needed. The institutional review board has confirmed that no ethical approval is required as it is a cross-sectional study. After creating the master chart, entered the data into Microsoft excel sheath and analyzed. Data are presented as mean (standard deviation).

RESULTS

All 120 patients had a history of COVID-19 disease in the last 6 months.

All patients had HbA1C above normal levels as depicted in Figure 1. The mean HbA1c was 9.7±2.3 % as depicted in Table 1 (p<0.001).

Serum ferritin levels were elevated in all patients as depicted in Figure 2. The mean serum ferritin was 539.6±484.9 ng/ as depicted in Table 1 (p<0.001).

Blood D-dimer levels were elevated in all patients as depicted in Figure 3. The mean D-dimer was 636.3±303.5 ng/mL as depicted in Table 1 (p<0.001).

Table 1: Patient details with HbA1c, serum ferritin, D-dimer levels.

Parameters	Mean±SD	P value
HbA1c	9.7±2.3	<0.001*
Serum ferritin	539.69±484.9	
D-dimer	636.34±303.5	

Where in "*p<0.001, highly significant at 1% level of significance".

Diabetes was detected in 94.1% of the patients. Among them 60.80% of patients had newly detected diabetes and 33.30% were known case of diabetes, 70.83% patients had a history of oral or intravenous steroid therapy, and 65% had any kind of use of steam or oxygen inhalation during COVID-19 treatment as depicted in Table 2 (p<0.001).

Table 2: Patient details with history of oxygen/steam inhalation, steroid use, diabetes mellitus.

Variables	Yes, N (%)	No, N (%)	Statistical test value	P value
History of oxygen/ steam inhalation	78 (28.3)	42 (50)	X^2=31.9	0.000*
History of steroid use	85 (30.8)	35 (41)		
Diabetes mellitus	113 (40.9)	7 (9)		
Total	276 (100)	84 (100)		

Where in "*p<0.001, highly significant at 1% level of significance."

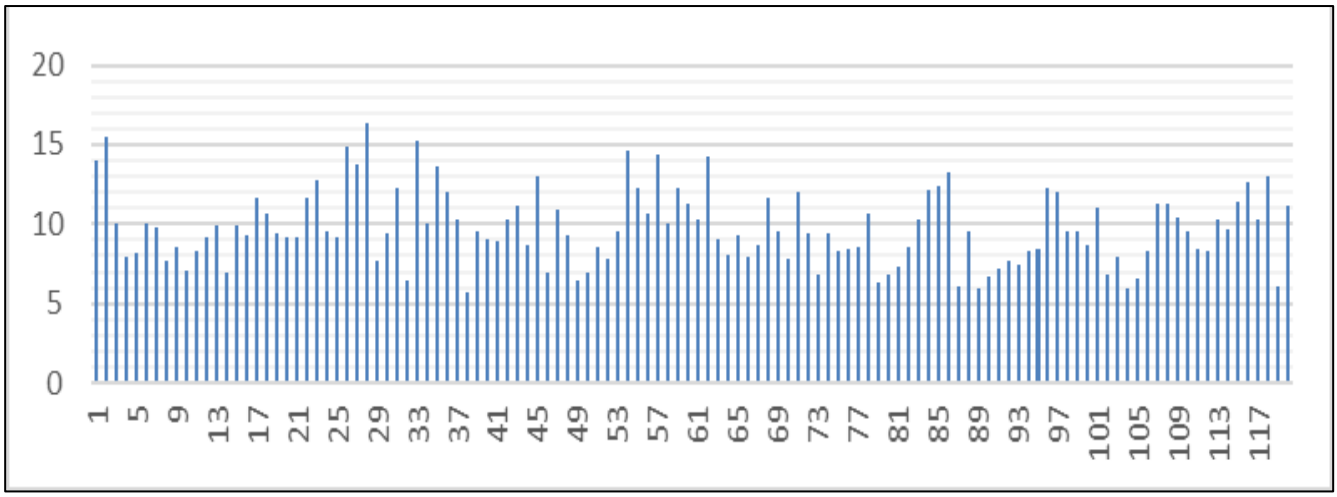

Figure 1: Line graph depicting HbA1c levels of the study group.

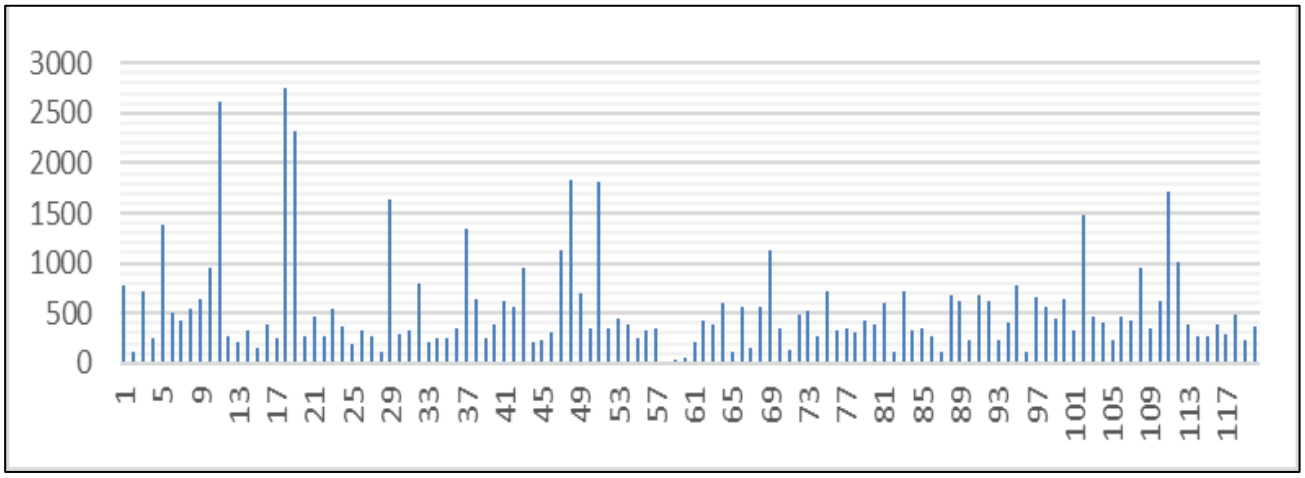

Figure 2: Line graph depicting serum ferritin levels of the study group.

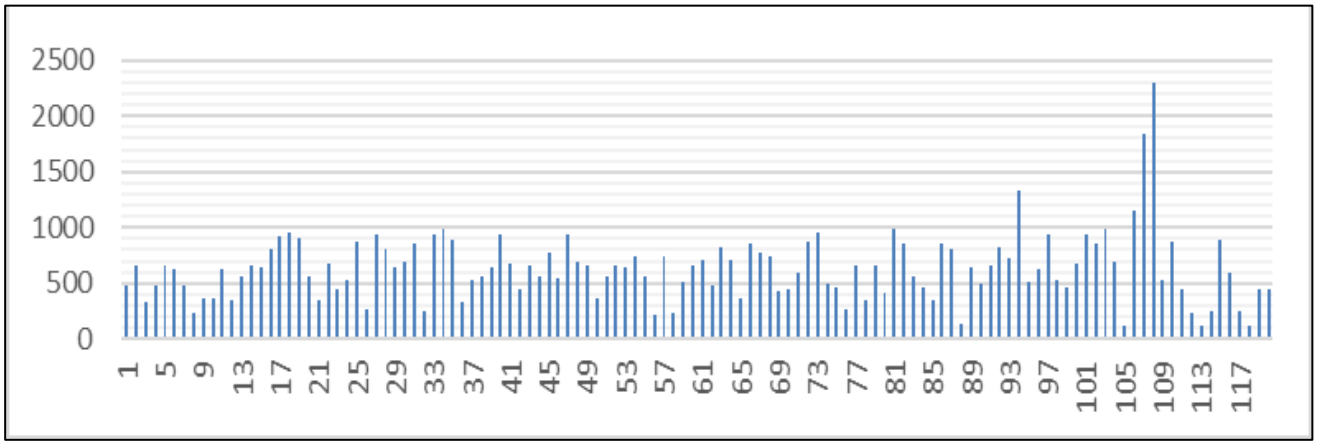

Figure 3: Line graph depicting D-dimer levels of the study group.

In all the above parameters p value was less than 0.001 which is highly significant at 1% level of significance.

DISCUSSION

The higher prevalence of mucormycosis in India could be due to many possible reasons such as the presence of a high load of Mucor spores in the hospital and community due to the tropical and humid climate, the high prevalence of uncontrolled diabetes cases, the large number of latent diabetes cases, poor regular health check-up and monitoring blood sugar levels, newly developed diabetes due to COVID-19 virus attack on pancreatic cells, poor monitoring of the dose and duration of steroids used to treat COVID-19 cases, and poor maintenance of frequently used oxygen mask.[7,8]

Patients with diabetes mellitus have a higher chance of suffering from COVID-19 associated mucormycosis seen in our study. In the present study 94.1% of the patients had diabetes mellitus. Among them 60.80% of the patients had newly detected diabetes and 33.30% were known cases of diabetes with mean HbA1c 9.7±2.3. A similar study done by Goddanti et al found that 36.66% had a history of recent onset diabetes mellitus and 59% had a history of chronic diabetes.[10] Four percentages subjects were non-diabetic. Raised glucose concentration and acidosis impede the phagocytic properties of neutrophils, thus weakening the immune response of the patient. This can be attributed to the fact that the hyperglycemia due to diabetes mellitus or secondary to steroid therapy in COVID-19 patients, is known to cause glycosylation of protein transferrin.

In COVID-19 infection there is a release of excessive of ferritin from cells due to cytokine stimulus by interleukin, especially IL-6, as an account of viremia there is significant activation of macrophages. The study observations made by Zhou et al, where ferritin levels of more than 400 correlated significantly with severe infection and mortality due to COVID-19.[9] Our study showed a mean range of serum ferritin of 539.6±484.9 which is higher. Goddanti et al did a similar study in the mean serum ferritin level was

461.31±26.38 which is above normal for either sex.[10] This is also similar with results of Spellberg et al who reported that greater serum ferritin levels were accompanied with significantly higher death rates.[11] Kell et al studied that ferritin arises from damaged cells, and can be raised significantly in response to inflammation or a variety of diseases that may explain the correlation of mortality with high serum ferritin level.[12]

In our study mean D-dimer range of 636.3±303.5, which is higher than normal. D-dimer is an indicator of cytokine storm and has an association with thrombotic phenomenon causing stroke, myocardial infarction, venous thrombosis, etc. Similar results were found in study by Goddanti et al in which 51.21% patients had elevated D-Dimer with mean value 671.99±52.94.[10] In similar study by Nayak et al, found high levels of D-Dimer with mean value of 761.33±151.8 ng/ml. Prior to the outbreak of the COVID-19 pandemic, D-dimer was not considered a useful biomarker for bacterial or viral pneumonia despite the evidence.[13]

In our study, we observed various non-independent factors also leading to the occurrence of COVID-19 associated mucormycosis viz; oxygen inhalation, steroid intake. We observed that 65% patients had history of any kind of use of steam or oxygen inhalation during their COVID-19 treatment. Similar results were found in study of Lenus et al in which 60% and in study of Goddanti et al 60% of patients had a history of oxygen usage during the period of COVID-19.[10,14] Improper sanitization of oxygen cylinders, lack of clean and distilled water in oxygen humidifiers, overuse of steam inhalation and humidified oxygen were put forth as some the possible precipitating factors for CAM.

In our study we observed that 70.83% had history of oral or intravenous use of steroid during COVID-19 management. Similar results were observed by Mishra et al in which 60% of CAM patients had a history of any kind of steroid use.[15] Also, Singh et al have reported 76.3% patients with history of steroid usage, and in the study of Kaneria MV et al it was found in 77.27% patients.[16,17]

The study is however limited as the baseline HbA1C levels of the diabetic patients prior to the COVID infection is not taken into account. Also, the effect of the multimodality treatment on levels of HbA1C, D-dimer, and ferritin needs to be assessed as it is likely to influence the aforementioned parameters.

CONCLUSION

This study shows that hyperglycaemia, iron overload, and elevated D-dimer levels with coexisting diabetes mellitus, use of steroids and use of oxygen significantly contribute to the pathogenesis of post-COVID mucormycosis, and timely correction of the aforementioned parameters can prevent the patients from further morbidity and mortality.

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