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Serum iron indices in COVID-19-associated mucormycosis: A case–control study

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Abstract

Background: Whether dysregulated iron metabolism is associated with COVID-19-associated mucormycosis (CAM) remains unknown. Herein, we compare the serum iron indices in COVID-19 subjects with and without mucormycosis.

Methods: We conducted a case–control study enrolling COVID-19 participants with and without mucormycosis. We compared the baseline serum iron indices (iron, ferritin, total iron-binding capacity [TIBC], unsaturated iron-binding capacity and percentage transferrin saturation) between CAM cases and COVID-19 controls. Additionally, we performed a multivariate logistic regression analysis to assess whether any iron indices are associated with CAM.

Results: We enrolled 28 CAM cases (mean age 53.6 years old; 78.6% men) and 26 controls (mean age 57.2 years old; 73.1% men). Rhino-orbital (±cerebral) mucormycosis (85.7%) was the most clinical presentation. Diabetes mellitus was more frequent in the cases than controls (75% vs. 42.3%; $p = .015$). Hypoxaemia during COVID-19 illness was more common in controls than cases. The mean serum iron values (33 vs. 45 μg/dl, $p = .03$) and TIBC (166.6 vs. 201.6 μg/dl, $p = .003$) were significantly lower in CAM cases than controls. On multivariate analysis, we found a lower TIBC (odds ratio [OR] 0.97; 95% confidence interval [CI], 0.95–0.99) and diabetes mellitus (OR 5.23; 95% CI, 1.21–22.68) to be independently associated with CAM after adjusting for serum iron, ferritin and glucocorticoid therapy. The case fatality rate of CAM was 73.9%. The iron indices were not significantly different between CAM survivors and non-survivors.

Conclusions: The CAM is associated with lower TIBC levels than COVID-19 subjects without mucormycosis, suggesting dysregulated iron metabolism in its pathogenesis. Further studies are required to confirm our preliminary observations.

KEYWORDS
aspergillosis, ferritin, invasive mould, iron, Mucorales, SARS-CoV, transferrin

1 | INTRODUCTION

Mucormycosis is a rapidly progressing angioinvasive disease caused by the fungi of the order Mucorales. The disease affects immune-suppressed individuals, including patients with neutropenia, uncontrolled diabetes mellitus, organ transplantation and others.[1] The emergence of COVID-19-associated mucormycosis (CAM) across several nations, particularly India, warrants a detailed research study to identify the potential contributing factors.[2–5] Several factors have been proposed for the emergence of CAM, although very few have been systematically evaluated.[6] Besides uncontrolled diabetes and inappropriate glucocorticoid therapy,[3] metabolism of trace elements, including zinc and copper, has been implicated for their possible roles in the pathogenesis of fungal infections in patients with COVID-19.[7,8]

The role of iron in promoting the growth of *Rhizopus* and the interplay of acidosis, hyperglycaemia and iron in mucormycosis has been elegantly demonstrated previously.[9,10] Decreased total iron-binding capacity (TIBC) has been linked to invasive fungal infections (candidiasis and invasive aspergillosis) in subjects with haematological malignancies.[11] Altered iron metabolism, especially elevated serum ferritin and low iron, has been reported in COVID-19 subjects.[12–14] Whether dysregulated iron metabolism is involved in the pathogenesis of CAM remains uncertain. We hypothesised that serum iron studies could vary in CAM versus COVID-19 subjects without mucormycosis, and their comparison might yield insights into the pathogenesis of CAM. The primary objective of the study was to compare the serum iron indices amongst COVID-19 subjects with and without mucormycosis and to ascertain the association of serum iron indices with CAM.

2 | METHODS

2.1 | Study design and setting

We performed a case–control study (April–May 2021) to evaluate the association between serum iron indices and COVID-19-associated mucormycosis. The Institute Ethics Committee approved our study protocol. We obtained written informed consent from the study participants or their next of kin. A part of the data has been previously published.[7]

2.2 | Study participants

We enrolled consecutive hospitalised subjects aged ≥18 years old from the emergency services of our hospital. Both the cases and controls were recruited during the same study period. The cases were subjects with a confirmed diagnosis of CAM. COVID-19 was diagnosed by reverse transcriptase-polymerase chain reaction for SARS-CoV-2 in nasopharyngeal or oropharyngeal swabs. We diagnosed mucormycosis in participants with compatible clinico-radiological features and confirmed microbiologically (aseptate hyphae on smears or culture showing growth of Mucorales) or pathologically in appropriate tissue samples. We arbitrarily defined CAM when mucormycosis was diagnosed concurrently or within 8 weeks of COVID-19 diagnosis. The controls were in-hospital participants with COVID-19 but without any evidence of mucormycosis. We followed up the controls for eight weeks after enrolment to ensure they had not developed mucormycosis.

We excluded the subjects where the diagnosis of mucormycosis could not be established by microbiology or histopathology and those with inadequate details.

2.3 | Objectives

The objectives were as follows: (1) to compare the serum iron indices amongst COVID-19 subjects with and without mucormycosis; (2) to evaluate whether iron indices were associated with the occurrence of CAM; and (3) to analyse the iron indices amongst survivors and non-survivors with CAM.

2.4 | Study procedure

We obtained the following information: (1) demographic profile, (2) details of any comorbid illnesses, (3) risk factors for mucormycosis (presence of diabetes, diabetic ketoacidosis [DKA], organ transplant, immunosuppressive therapy or others), (4) the extent of hypoxaemia and management (nature and duration of respiratory support provided and details of the treatment instituted) during COVID-19, (5) laboratory parameters at the time of admission including complete blood count, arterial blood gas analysis, liver, renal function tests and serum iron profile (serum iron, serum ferritin, TIBC, unsaturated iron-binding capacity [UIBC] and per cent transferrin saturation [TSat%]) and (6) outcome at discharge from hospital. For the CAM cases, we also noted the time elapsed between COVID-19 and mucormycosis, the site of involvement and the diagnostic test used for confirmation.

2.4.1 | Serum iron, TIBC and TSat%

We collected 3 ml of peripheral venous blood and separated the serum. We used a fully automated EM Destiny 180 biochemical analyser (Transasia India Ltd) based on the spectrophotometric measurement of coloured derivatives. For serum iron, the linear measuring range of the kit is 8.66–890 μg/dl, and the precision of the test (coefficient of variation [CV]) is 1.78%–3.34%. The normal range for adult men and women is 65–175 μg/dl and 50–170 μg/dl, respectively. For measuring the serum UIBC, the linear measuring range is 12.2–890 μg/dl with a precision (CV) of 2.35%–4.58%. The normal range of UIBC is 110–370 μg/dl.

The serum TIBC (normal range, 228–428 μg/dl) was calculated by adding serum iron and UIBC. The TSat% (normal range 20%–40%)

was calculated as serum iron multiplied by 100 and divided by TIBC. We assayed serum ferritin on a fully automated Cobas e411 electrochemiluminescence-based immunoanalyser (Roche Diagnostics). The measuring range of the kit is 0.5–2000 μg/L (or ng/ml), and the values above the measuring range (>2000 μg/L) were retested after 1:50 dilution. The precision (CV) of the test is 6.7%–11.6%. The normal range in men and women is 30–400 μg/L and 13–150 μg/L, respectively.

2.5 | Statistical analysis

We used the commercially available statistical software package SPSS 22.0 (IBM SPSS, Inc.) for our analysis. The categorical variables are presented as numbers with percentages and continuous variables as mean with a 95% confidence interval. We compared the differences between categorical and continuous variables using the chi-square test and the Mann–Whitney *U* test, respectively. We performed a multivariate logistic regression analysis to determine the factors associated with CAM.

3 | RESULTS

3.1 | Baseline features and outcome of study participants

We identified 59 participants; of whom, five were excluded due to missing details. Finally, we included 28 cases and 26 controls (Table 1). The mean age of cases and controls was 53.6 and 57.2 years old, respectively. Most subjects were men (78.6% cases, 73.1% controls). Diabetes mellitus was seen more often in cases (75% vs. 42.3%, $p = .015$). The proportion of subjects with newly diagnosed diabetes mellitus or DKA was not significantly different in the two groups. None of the subjects reported using iron supplementation or iron chelator. There was no difference in the complete blood count, liver and renal functions, or arterial pH amongst cases and controls.

During COVID-19 illness, hypoxaemia was more frequent in the controls than in the cases (96.2% vs. 57.1%, respectively; $p = .001$). About 31.5% of the study subjects were mechanically ventilated, and the proportion was not different between the groups ($p = .10$). The mean duration of glucocorticoid therapy was 10.6 and 7 days amongst cases and controls, respectively ($p = .06$). Rhino-orbito-cerebral site (53.5%) was the most common site of mucormycosis, followed by the rhino-orbital site (32.1%) and pulmonary site (14.3%). The mean duration of hospitalisation amongst cases was 8.3 days versus 12 days amongst controls ($p = .66$). Mortality amongst CAM subjects was 73.9%.

3.2 | Serum iron indices

The median serum iron level was significantly lower in the cases than the controls (33 vs. 45 μg/dl, $p = .03$) (Figure 1). Serum ferritin was elevated in both cases and controls (1446 and 1246 ng/ml, $p = .42$). The serum TIBC was significantly lower ($p = .003$) in the cases (166.6 μg/dl) than the controls (201.6 μg/dl). The UIBC and TSat% values were not statistically different between cases and controls.

3.3 | Factors associated with the development of mucormycosis in COVID-19

On multivariate analysis, a lower TIBC and the presence of diabetes mellitus were independently associated with CAM after adjusting for other factors (Table 2).

3.4 | Survivors and non-survivors with CAM

Amongst subjects with CAM, 17 of the 23 (for whom data were available) died within 4 weeks of diagnosis. None of the serum iron indices were significantly different amongst survivors and non-survivors with CAM (Table 3).

4 | DISCUSSION

We found a significantly lower serum iron and TIBC in CAM subjects than COVID-19 subjects without mucormycosis. On a multivariate model, lower TIBC and diabetes mellitus were independently associated with CAM after adjusting serum iron, ferritin and glucocorticoid therapy for COVID-19. None of the serum iron indices (iron, ferritin, TIBC or TSat%) were significantly different between survivors and non-survivors with CAM.

The role of iron in the development of mucormycosis has been convincingly demonstrated in diabetic mice models.[15,16] However, there are little clinical data on the association of mucormycosis (COVID or non-COVID) with serum iron indices. A post hoc analysis of 20 patients with mucormycosis enrolled in the DEFEAT mucor trial found serum iron within the normal range. Nevertheless, subjects with a higher baseline serum iron ≥72 mg/dl and serum ferritin ≥2700 mg/dl had greater 90-day mortality (univariate analysis).[17] The DEFEAT mucor study did not have a control arm without mucormycosis, and most subjects with higher baseline serum iron had haematologic malignancy. In the absence of any case–control study evaluating various iron indices in mucormycosis, we cannot compare our results with any prior human data.

In a murine mucormycosis model, a lower UIBC due to DKA promoted the growth of *Rhizopus arrhizus*.[15] The association of lower TIBC with invasive fungal infections (candidiasis and invasive aspergillosis) has been previously shown in acute leukaemic patients with chemotherapy-induced neutropenia.[11] Karp and Merz performed serial TIBC values in leukaemic patients undergoing chemotherapy and observed that the nadir of TIBC coincided with the most severe neutropenia. Furthermore, TIBC returned to baseline levels when the neutropenia normalised. Also, patients responding to amphotericin

TABLE 1 Baseline characteristics of coronavirus disease (COVID-19) subjects with and without mucormycosis (cases and controls, respectively)

	Cases ($n = 28$)	Controls ($n = 26$)	p value
Age, years	53.6 (48.2–59.1)	57.2 (52.1–62.4)	0.33
Male sex	22/28 (78.6)	19/26 (73.1)	0.64
Risk factors			
Diabetes mellitus	21/28 (75)	11/26 (42.3)	0.015
Newly diagnosed at this admission	5/21 (23.8)	1/11 (9.1)	0.64
Duration of diabetes mellitus, years[a]	7.1 (4.1-10.2)	6.0 (1.5–10.5)	0.86
Diabetic ketoacidosis	9/21 (42.9)	4/11 (36.4)	1.00
Glycated haemoglobin, %	11.3 (9.4-13.3)	9.2 (6.8–11.6)	0.14
Haematological malignancy	0	1/26 (3.8)	0.48
COVID-19 and its management			
Hypoxaemia	16/28 (57.1)	25/26 (96.2)	0.001
Mechanical ventilation for COVID-19	6/28 (21.4)	11/26 (42.3)	0.10
Glucocorticoids	19/27 (70.4)	19/24 (79.2)	0.47
Duration of glucocorticoid therapy, days	10.6 (7.2-14.0)	7.0 (5.4–8.6)	0.06
Site of mucormycosis			
Rhino-orbital	9/28 (32.1)	-	
Rhino-orbito-cerebral	15/28 (53.6)	-	
Pulmonary	4/28 (14.3)	-	
Investigations			
Haemoglobin, g/dl	12.5 (11.6–12.9)	12.0 (11.1–12.9)	0.46
Total leucocyte count, cells/μl	15,953 (13,238–18,669)	15,421 (12,493–18,351)	0.79
Lymphocyte (%)	6 (4–8)	10 (4–16)	0.22
Platelet count, $\times 10^3$ cells/μl	249 (204–295)	213 (172–254)	0.23
Serum creatinine, mg/dl	1.5 (0.9–2.1)	2.4 (1.0–3.8)	0.25
Serum bilirubin, mg/dl	0.7 (0.6–0.9)	0.6 (0.5–0.8)	0.34
Serum albumin, mg/dl	2.9 (2.7–3.1)	3.1 (2.9–3.5)	0.09
Arterial pH	7.39 (7.34–7.45)	7.40 (7.36–7.44)	0.83
Serum bicarbonate, mmol/L	17.6 (15.0–20.1)	19.7 (16.6–22.7)	0.28
Iron profile[b]			
Serum iron, μg/dl	33.3 (23.8–61.4)	45 (23.8–61.4)	0.03
Serum ferritin, ng/ml	1446 (770–2973)	1246 (452–2980)	0.42
Total iron-binding capacity, μg/dl	166.6 (124.4–188.3)	201.6 (164.3–233.7)	0.003
Unsaturated iron-binding capacity, μg/dl	106.3 (94.4–146.8)	124.8 (104.8–185.4)	0.07
Percentage transferrin saturation, %	24.4 (13.4–37.6)	23.5 (16.6–39.8)	0.63
Outcome			
Duration of hospitalisation, days	8.3 (4.8–11.8)	12.0 (7.3–16.7)	0.66
Survival duration,[c] days	16.0 (9.5–22.6)	18.0 (11.9–24.0)	0.19
Mortality[c]	17/23 (73.9)	17/26 (65.4)	0.52

Abbreviation: CAM, COVID-19-associated mucormycosis.

The values are presented as mean (95% confidence interval) or numbers (percentage).

[a]Mean duration of diabetes mellitus excluding subjects diagnosed during the current admission.

[b]For data that were not normally distributed, the values are presented as median (1st quartile–3rd quartile).

[c]Outcome data were not available for five cases of CAM.

therapy showed faster improvement in TIBC values, whilst TIBC declined in non-responders.[11] The median TIBC in this study was below the laboratory reference for both cases and controls. TIBC was also significantly lower in cases than controls. The TIBC values in our CAM cases were like that of patients with fungal infections in the study by Karp and Merz.[11] The lower iron-binding capacity

observed in the CAM cases may denote the poor binding of iron to transferrin and increased availability of iron for the pathogenic fungi. Our study is the first to demonstrate the association of lower TIBC in mucormycosis or CAM.

Acidosis of any cause promotes dissociation of iron from transferrin, and the increased iron availability promotes the growth of microorganisms, particularly Mucorales.[9,16] Furthermore, iron and DKA increase the endothelial expression of a 78 kDa glucose-regulated protein (GRP78)[18,19] and its ligand Cot H3 on *Rhizopus*. High GRP78 levels have also been reported in COVID-19.[20] Interestingly, the mean arterial pH in our study was not acidotic in both cases and controls. The proportion of subjects with DKA in our study was also similar in both our study groups.

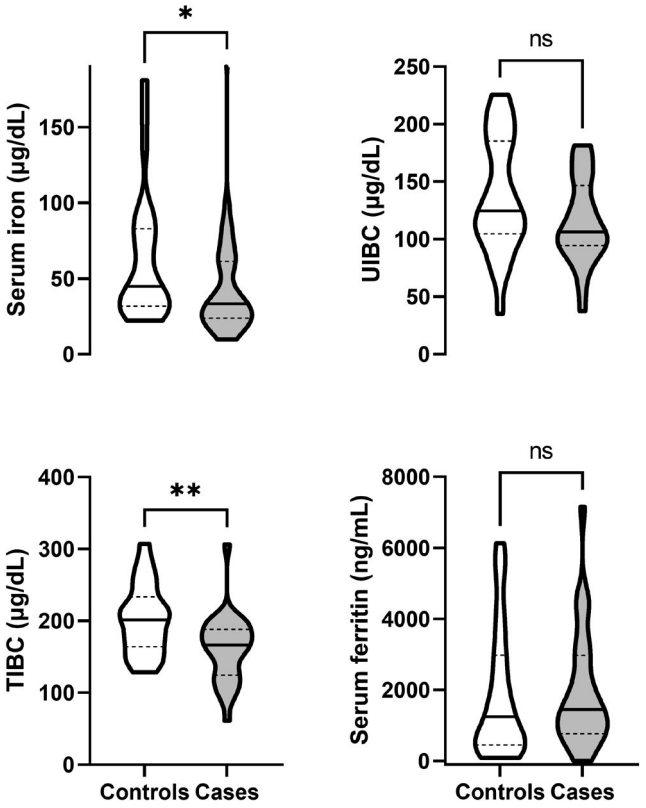

FIGURE 1 Violin plot (truncated) showing the distribution of serum iron, unsaturated iron-binding capacity (UIBC), total iron-binding capacity (TIBC) and serum ferritin amongst COVID-19 subjects with (cases; shaded in grey) and without mucormycosis (controls). The width of the violin plot is determined by the number of data points corresponding to different levels of test values. The solid central line in each graph shows the median value, whilst the dotted line below and above the median represents the first and third quartiles, respectively. Serum iron and TIBC were significantly lower in the cases than in the controls. *p =.03 and **p =.003

We observed low serum iron in both cases and controls, contrary to our expectations. Hepcidin, an acute phase reactant produced by the liver, is upregulated during infections (including COVID-19)[21] and inflammation.[22] An elevated hepcidin and accompanying low serum iron have been associated with severe respiratory failure and mortality in COVID-19.[23–25] Whilst a low serum iron could confer 'nutritional immunity' by limiting iron availability to pathogens,[22,26] it may also lead to a dysregulated immune system and impair responses to hypoxia.[22] We found elevated serum ferritin and low serum iron, suggesting an ongoing inflammation. However, the ferritin values were similar in the cases and controls. Recently, Bhanuprasad et al compared CAM with non-COVID mucormycosis and found elevated ferritin levels in the former.[27] There is, however, no clear explanation for the significantly lower serum iron levels in CAM than controls in our study. Notably, the controls were more often hypoxaemic than CAM cases, where one expects lower serum iron levels. We can also speculate that CAM subjects were unwell longer, had chronic inflammation and had iron indices consistent with anaemia of inflammation (chronic disease). However, the serum ferritin levels were similar in both cases and controls. Another intriguing possibility could be increased iron consumption by Mucorales during CAM development. Finally, the observation could be a chance occurrence.

The mortality of mucormycosis in this study was higher than the previously published experience with CAM[3,28] and non-COVID mucormycosis.[29,30] This study was conducted during the peak of the devastating second wave of the COVID-19 pandemic and CAM epidemic in India. The shortage of diagnostic resources, hospital beds and antifungal drugs could be additional factors accounting for the increased mortality in CAM subjects.[5] Moreover, nearly two-thirds of the CAM subjects had rhino-orbito-cerebral (53%) and pulmonary (14%) involvement, sites known to have higher mortality.[17,31]

Finally, our study is not without limitations. The major limitation is the small number of cases and controls from a single centre. We could evaluate only a few parameters of interest in the multivariate model, and there could be confounding factors. We enrolled hospitalised controls, and the choice of controls with severe disease could have influenced the serum iron indices. We did not measure

TABLE 2 Multivariate logistic regression analysis showing the factors associated with the development of mucormycosis in COVID-19 patients

Variables	Cases	Controls	Odds ratio (95% confidence interval)	*p*-value
Diabetes mellitus	21/28 (75)	11/26 (42.3)	5.234 (1.208–22.678)	0.027
Glucocorticoids	19/27 (70.4)	19/24 (79.2)	0.489 (0.100–2.398)	0.38
Serum iron, µg/dl	33.3 (23.8–61.4)	45 (23.8–61.4)	1.013 (0.992–1.035)	0.22
Total Iron binding capacity, µg/dl	166.6 (124.4–188.3)	201.6 (164.3–233.7)	0.974 (0.953–0.996)	0.019
Serum ferritin, ng/ml	1446 (770–2973)	1246 (452–2980)	1.000 (0.999–1.000)	0.23

Note: The values or presented as numbers/total number (percentage) or median (1st–3rd quartile).

TABLE 3 Clinical and laboratory parameters of survivors and non-survivors of coronavirus disease (COVID-19)-associated mucormycosis

	Survivors ($n = 6$)	Non-survivors ($n = 17$)	p value
Age, years	49.5 (40.3–58.7)	53.9 (45.9–61.9)	0.52
Male sex	5/6 (83.3)	14/17 (82.4)	1.0
Mean duration of COVID-19 positivity to CAM	6.7 (−2.7 to 20.7)	2.4 (−3.7 to 8.6)	0.46
Risk factors			
Diabetes mellitus	5/6 (83.3)	13/17 (76.5)	1.0
Diabetic ketoacidosis	1/6 (16.7)	7/17 (41.2)	0.36
COVID-19 and its management			
Hypoxaemia at presentation	1/6 (16.7)	13/17 (76.5)	0.002
Mechanical ventilation for COVID-19	0	6/17 (35.2)	0.30
Glucocorticoids	2/6 (33.3)	13/16 (81.3)	0.03
Site of mucormycosis			0.12
Rhino-orbital	3/6 (50)	4/17 (23.5)	
Rhino-orbito-cerebral	1/6 (17.7)	11/17 (64.7)	
Pulmonary	2/6 (33.3)	2/17 (11.8)	
Investigations			
Haemoglobin, g/dl	11.6 (9.4–13.8)	12.5 (11.7–13.9)	0.47
Lymphocyte (%)	8 (−1 to 18)	5 (2–8)	0.39
Serum creatinine, mg/dl	1.8 (−0.2 to 3.8)	1.56 (0.7–2.4)	0.78
Serum albumin, mg/dl	3.0 (2.4–3.6)	2.7 (2.5–2.9)	0.16
Arterial pH	7.37 (7.17–7.57)	7.39 (7.31–7.47)	0.79
Serum bicarbonate, mmol/L	14.5 (10.7–18.3)	17.2 (13.7–20.6)	0.49
Iron profile[a]			
Serum iron, μg/dl	26.7 (25.6–39)	33.9 (20.8–71.2)	0.73
Serum ferritin, ng/ml	1128 (579–1865)	1757 (880–3947)	0.23
Total iron-binding capacity, μg/dl	184.5 (143–192.5)	155 (121.9–188.5)	0.33
Unsaturated iron-binding capacity, μg/dl	156.3 (93.1–165.9)	102.4 (83–122.1)	0.16
Percentage transferrin saturation, %	15.9 (13.1–27.2)	14.3 (26.4–39.4)	0.29
Outcome			
Mean duration of hospitalisation, days	18.0 (3.1–32.9)	5.9 (3.9–7.9)	0.004
Mean duration of survival, days	38.5 (30.9–46.1)	8.1 (4.9–11.3)	0.0001

Note: The values are presented as mean (95% confidence interval) or numbers (percentage).

Abbreviation: CAM, COVID-19-associated mucormycosis.

[a]For data that were not normally distributed, the values are presented as median (1st quartile–3rd quartile).

hepcidin levels in our study and hence cannot exclude or quantitate the influence of inflammation on the iron indices. Furthermore, we measured the iron indices after the development of mucormycosis and not during COVID-19 illness. Hence, there may have been differences in iron indices amongst the COVID-19 controls and CAM cases. We also do not have serial TIBC levels. Animal models and serial measurement of iron indices in prospective cohorts may provide deeper insights into the pathophysiology of CAM. Our study, however, provides vital information on a relatively unexplored area that needs to be pursued further.

In conclusion, our preliminary findings showed significantly lower serum TIBC in CAM cases than in the controls, suggesting a potential association of altered iron haemostasis in CAM. More extensive clinical and animal studies are required to validate our results.

CONFLICT OF INTEREST

The author declares that there is no conflict of interest.

AUTHOR CONTRIBUTION

Mohan Kumar H: Data curation (equal); Formal analysis (equal); Investigation (supporting); Methodology (equal); Project administration (equal); Resources (supporting); Writing – original draft (equal); Writing – review and editing (equal). **Prashant Sharma:** Data curation (supporting); Investigation (lead); Methodology (supporting); Validation (supporting); Writing – review and editing (supporting). **Shivaprakash M. Rudramurthy:** Data curation (supporting); Investigation (supporting); Project administration (supporting); Resources (supporting); Writing – review and editing (supporting). **Inderpaul S. Sehgal:** Data curation (supporting);

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DATA AVAILABILITY STATEMENT

Additional data is available from the corresponding author on request.

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