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Occurrence of hypoalbuminemia in cases of rhino-orbito-cererbral mucormycosis and its relationship with the disease severity according to staging, a tertiary care center-based study

Shyamash Mandal[1], Monoj Mukherjee[2], Satish Reddy Satty[3], Souvik Das[4], Atanu Chandra[5]

[1,5]Assistant Professor, [4]Post Graduate Trainee, Department of General Medicine, [2]Associate Professor and Head, [3]Senior Resident, Department of Otorhinolaryngology, Bankura Sammilani Medical College and Hospital, Bankura, West Bengal, India

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ABSTRACT

Background: Mucormycosis is a serious but rare fungal infection with increasing incidence of rhino-orbito-cerebral mucormycosis (ROCM) in the setting of COVID-19. Some studies have shown presence of hypoalbuminemia in cases of mucormycosis, which can affect the prognosis, outcome, and also the drug toxicity in a significant way. A staging of ROCM was proposed and is being used widely based on clinical symptoms and signs, evaluation, and diagnosis. **Aims and Objectives:** Our objective was to look for any relationship between two factors, occurrence of hypoalbuminemia and severity of ROCM according to staging. **Materials and Methods:** The study was a hospital-based prospective cross-sectional study done on 41 ROCM patients. All patients of diagnosed ROCM were included by complete enumeration method. Serum albumin of every patient was measured using standard biochemical procedures and patients were divided into groups of normoalbuminemia (Serum albumin level >3.5 gm/dl), mild hypoalbuminemia (Serum albumin level 2.5–3.5 gm/dl), and severe hypoalbuminemia (Serum albumin level <2.5 gm/dl). All the patients were divided into Stage 1, 2, 3, and 4 according to severity of ROCM. Then, the occurrence of hypoalbuminemia was calculated among the patients and correlation between ROCM stages and severity of hypoalbuminemia was measured using standard statistical tools. **Results:** Among the patients of ROCM, 15% patients did not develop any hypoalbuminemia. About 51% developed mild hypoalbuminemia and 34% developed severe hypoalbuminemia. Maximum number of severe hypoalbuminemia patients were found in the Stage 3 group [total 6 (35%)], but the incidence of the same was maximum in the Stage 4 group (56%). Mild hypoalbuminemia is most common (10) and also most prevalent in the Stage 3 group (59%). **Conclusion:** We found out that serum albumin level is significantly affected by ROCM severity, that is, more severe the disease, more chance to develop hypoalbuminemia.

Key words: Rhino-orbito-cerebral mucormycosis; Hypoalbuminemia; Severity; Staging; Relationship

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INTRODUCTION

Mucormycosis is a potentially lethal, angioinvasive fungal infection predisposed by diabetes mellitus, corticosteroids and immunosuppressive drugs, primary or secondary immunodeficiency, hematological malignancies and hematological stem cell transplantation, solid organ malignancies, and solid organ transplantation

Address for Correspondence:
Dr. Souvik Das, Post Graduate Trainee, Department of General Medicine, Bankura Sammilani Medical College and Hospital, Bankura - 722 102, West Bengal, India. **Mobile:** 7980102768/7685939885. **E-mail:** iamsouvik1008@gmail.com

and iron overload.[1,2] The increasing incidence of rhino-orbito-cerebral mucormycosis (ROCM) in the setting of COVID-19 in India and elsewhere has become a matter of immediate concern.[3-5] From the time that a series of six cases of ROCM were reported in February 2020, there has been an exponential increase in incidence in India with the soaring second wave of COVD-19.[2,6] ROCM being a rapidly progressive disease, even a slight delay in the diagnosis or appropriate management can have devastating implications on patient survival.[7] However, the outcome can be optimized by early diagnosis prompted by awareness of warning signs and symptoms and high index of clinical suspicion, confirmation of diagnosis by appropriate modalities, and initiation of aggressive medical and surgical treatment by a multidisciplinary team.[7,8]

A study conducted by Banerjee et al. (in the source there is a review authored by Sayantan Banerjee, David W. Denning and Arunaloke Chakrabarti), revealed that India's overall mucormycosis prevalence was around 0.14 cases/1000 population in India.[9] The overall mortality in mucormycosis when well-treated ranges from 30% to 46.7%. This could translate to about 105,000 people succumbing to these infections every year in the WHO southeast Asian region, were these numbers to be applied to the region.

ROCM can be categorized as possible, probable, and proven. A patient who has symptoms and signs of ROCM in the clinical setting of concurrent or recently (<6 weeks) treated COVID-19, diabetes mellitus, use of systemic cortico-steroids and tocilizumab, mechanical ventilation, or supplemental oxygen is considered as Possible ROCM. When the clinical symptoms and signs are supported by diagnostic nasal endoscopy findings, or contrast-enhanced MRI or CT scan, the patient is considered as Probable ROCM. Clinicoradiological features, coupled with microbiological confirmation on direct microscopy or culture or histopathology with special stains or molecular diagnostics, are essential to categorize a patient as Proven ROCM.

Staging of ROCM

The staging system of ROCM is simple and follows the general anatomical progression of ROCM from the point of entry (nasal mucosa) to the paranasal sinuses, orbit, and brain, and severity in each of these anatomical locations. According these factors, ROCM is divided into four stages, Stage 1, 2, 3, and 4.

Aims and objectives

Our objective was to look for any relationship between two factors, occurrence of hypoalbuminemia and severity of ROCM according to staging. If there is a statistically significant association between these two factors, then hypoalbuminemia might be used as a surrogate marker of screening of ROCM and prompt and aggressive management of hypoalbuminemia can significantly and favorably alter the outcome of the disease, especially when surgical intervention is indicated.

MATERIALS AND METHODS

It is a prospective cross-sectional study, done in patients admitted in ward of the Department of Otorhinolaryngology, Critical Care Unit, COVID ward under Department of General Medicine, B.S.M.C.H, Bankura. Final permission from the Institutional Ethical Committee of our institution was obtained before data collection. All patients of diagnosed ROCM are included by complete enumeration method. All the cases of ROCM diagnosed both clinically and histopathologically, in the in-patient ward of Department of Otorhinolaryngology, Critical Care Unit, COVID ward under Department of General Medicine, B.S.M.C.H, Bankura, were included. Known or diagnosed cases of chronic kidney disease, diabetic nephropathy, uncontrolled hypertension, and chronic liver disease were excluded from the study. All the cases of ROCM are treated according to their situation and other associated conditions according to standard protocol. All the patients are treated with 20% Human albumin according to standard protocol (Infusion 20% Human Albumin at a rate of 20 drops per minute once daily). Serum albumin value is repeated every 3 days interval. Treatment continued until serum albumin reaches 3.5 gm/dl or the patient has expired. For the purpose of data analysis soft-ware package, for example, SPSS version 22 is used as required value of <0.05 will be considered significant at 95% confidence limit.

RESULTS

Total 41 patients of diagnosed ROCM were taken into our study, 5 (12%) out of them were included in Stage 1, 10 (24%) were in Stage 2, 17 (42%) were in Stage 3, and 9 (22%) were in Stage 4.

Among the 41 patients of ROCM, 6 (15%) patients did not develop any hypoalbuminemia, whereas 21 (51%) developed mild hypoalbuminemia (serum albumin level 2.5–3.5 gm/dl) and 14 (34%) developed severe hypoalbuminemia (serum albumin level <2.5 gm/dl) (Table 1).

Table 1: Total number patients of ROCM grouped according to serum albumin status

Serum albumin level (in gm/dl).	>3.5	2.5–3.5	<2.5	Total
Total number of patients	6	21	14	41

Table 2: Relation between ROCM stages and hypoalbimunemia severity

ROCM Staging. Sr albumin level	Stage 1	Stage 2	Stage 3	Stage 4	Row Total
<2,5	1	2	6	5	14
2.5-3.5	1	7	10	3	21
>3.5	3	1	1	1	6
Column total	5	10	17	9	41

Table 2 and Diagram 1 show that among the Stage 1 ROCM patients, 20% developed severe hypoalbuminemia, 20% developed mild hypoalbuminemia, and 60% of patients had their serum albumin level >3.5 g/dl throughout their disease course. Among Stage 2 patients, 20% developed severe hypoalbuminemia, 70% developed mild hypoalbuminemia, and 10% had no hypoalbuminemia at all. Among Stage 3 patients, the mild hypoalbuminemia was most common (59%) and among Stage 4 patients, most prevalent was severe hypoalbuminemia (56%). It is evident that as the severity of ROCM rises, it worsens the serum albumin status of the patient (Tables 3 and 4). Maximum number of severe hypoalbuminemia patients were found in the Stage 3 group [total 6 (35%)], but the incidence of the same was maximum in the Stage 4 group (56%). Mild hypoalbuminemia is most common (10) and also most prevalent in the Stage 3 group (59%).

Table 3 shows the relationship between serum albumin level and ROCM staging. Within braces are the individual P values of each section. Chi-square statistics is 9.5408. P-value is 0.022902. The result is significant at $P<0.05$.

Table 4 shows the Chi-square statistics of the relationship of stages and hypoalbuminemia is 2.9977. P-value is 0.391982. The result is not significant at $P<0.05$.

Table 3: Relationship between Serum albumin level and ROCM severity

ROCM Stage	Serum albumin level (gm/dL)	
	≥3.5 (Normoalbuminemia)	<3.5 (Hypoalbuminemia)
Stage 1	3 (7.03)	2 (1.21)
Stage 2	1 (1.46)	9 (0.03)
Stage 3	1 (0.89)	16 (0.15)
Stage 4	1 (0.08)	8 (0.01)

Table 4: Relationship of ROCM staging with stages of hypoalbuminemia. Within braces are *P* values of individual sections

	Serum albumin level (gm/dL)	
ROCM Stage	2.5–3.5	<2.5
Stage 1	1 (0.05)	1 (0.03)
Stage 2	2 (0.71)	7 (0.47)
Stage 3	6 (0.03)	10 (0.02)
Stage 4	5 (1.01)	3 (0.68)

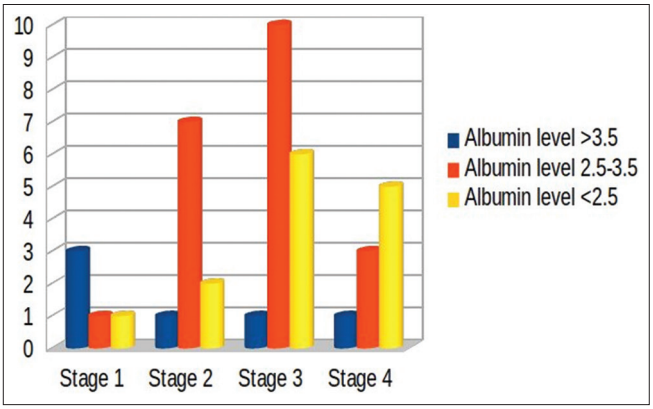

Diagram 1: Relationship between ROCM stages and hypoalbuminemia severity

DISCUSSION

Albumin, a 66.5 kilodaltons globular protein, has a number of important physiologic functions, which include maintaining oncotic pressure, transporting various agents (fatty acids, bile acids, cholesterol, metal ions, and drugs), scavenging free oxygen radicals, acting as an antioxidant, and exerting an antiplatelet effect. Synthesis of albumin takes place in the liver and hypoalbuminemia in adults, defined by an intravascular albumin level of <3.5 g/dl, is associated with poor post-operative outcomes in patients undergoing surgical intervention.[10] Three theoretical constructs might explain this relationship. First, albumin might serve as a nutritional marker such that hypoalbuminemia represents poor nutritional status in patients who go on to experience poor post-operative outcomes. Second, albumin has its own pharmacologic characteristics as an antioxidant or transporter, and therefore, the lack of albumin might result in a deficiency of those functions, resulting in poor post-operative outcomes. Albumin also acts as the most significant modulator of plasma oncotic pressure and functions to transport a variety of ligands, including bilirubin, calcium, fatty acids, and drugs such as mehadone, propranolol, thiopental, furosemide, warfarin, methotrexate, alfentanil, and many others.[11] Third, albumin is known to be a negative acute phase protein, and as such hypoalbuminemia might represent an increased inflammatory status of the patient, potentially

Proposed Staging of Rhino-Orbito-Cerebral Mucormycosis (ROCM)

Staging of Rhino-Orbito-Cerebral Mucormycosis	Symptoms	Signs	Primary Assessment	Confirmation of Diagnosis
Stage 1: Involvement of the nasal mucosa 1a: Limited to the middle turbinate 1b: Involvement of the inferior turbinate or ostium of the nasolacrimal duct 1c: Involvement of the nasal septum 1d: Bilateral nasal mucosal involvement	Nasal stuffiness, nasal discharge, foul smell, epistaxis	Foul-smelling sticky mucoid or black-tinged, or granular or haemorrhagic nasal discharge, nasal mucosal inflammation, erythema, violaceous or blue discoloration, pale ulcer, anaesthesia, ischemia, eschar	Diagnostic nasal endoscopy, Contrast-enhanced MRI (preferred) or CT-scan	Deep nasal swab or endoscopy-guided nasal swab or nasal mucosal biopsy for direct microscopy, culture and molecular diagnostics; nasal mucosal biopsy for rapid histopathology with special stains
Stage 2: Involvement of paranasal sinuses 2a: One sinus 2b: Two ipsilateral sinuses 2c: > Two ipsilateral sinuses and/or palate/oral cavity 2d: Bilateral paranasal sinus involvement or involvement of the zygoma or mandible	Symptoms in Stage 1 + facial pain, facial edema, dental pain, systemic symptoms (malaise, fever)	Signs in Stage 1 + unilateral or bilateral, localized or diffuse facial edema, edema localized over the sinuses, localized sinus tenderness	Diagnostic nasal endoscopy, Contrast-enhanced MRI (preferred) or CT-scan	Same as Stage 1 + sinus biopsy for direct microscopy, culture and molecular diagnostics and rapid histopathology
Stage 3: Involvement of the orbit 3a: Nasolacrimal duct, medial orbit, vision unaffected 3b: Diffuse orbital involvement (>1 quadrant or >2 structures), vision unaffected 3c: Central retinal artery or ophthalmic artery occlusion or superior ophthalmic vein thrombosis; involvement of the superior orbital fissure, inferior orbital fissure, orbital apex, loss of vision 3d: Bilateral orbital involvement	Symptoms in Stage 1 and 2 + pain in the eye, proptosis, ptosis, diplopia, loss of vision, infraorbital and facial V1 V2 nerve anesthesia	Signs in Stage 1 and 2 + conjunctival chemoses, isolated ocular motility restriction, ptosis, proptosis, infraorbital nerve anesthesia, central retinal artery occlusion, features of ophthalmic artery occlusion and superior ophthalmic vein thrombosis. V1 and V2 nerve anesthesia, and features of III, IV and VI nerve palsy indicating orbital apex/superior orbital fissure involvement.	Diagnostic nasal endoscopy, Contrast-enhanced MRI (preferred) or CT-scan	Same as Stage 2 + orbital biopsy if indicated and if feasible (if the disease is predominantly orbital) for direct microscopy, culture and molecular diagnostics and rapid histopathology
Stage 4: Involvement of the CNS 4a: Focal or partial cavernous sinus involvement and/or involvement of the cribriform plate 4b: Diffuse cavernous sinus involvement and/or cavernous sinus thrombosis 4c: Involvement beyond the cavernous sinus, involvement of the skull base, internal carotid artery occlusion, brain infarction 4d: Multifocal or diffuse CNS disease	Symptoms in Stage 1 to 3 + bilateral proptosis, paralysis, altered consciousness, focal seizures	Signs in Stage 1-3 (some features overlap with Stage 3) + V1 and V2 nerve anesthesia, ptosis, and features of III, IV and VI nerve palsy indicate cavernous sinus involvement. Bilaterality of these signs with contralateral orbital edema with no clinico-radiological evidence of paranasal sinus or orbital involvement on the contralateral side indicate cavernous sinus thrombosis. Hemiparesis, altered consciousness and focal seizures indicate brain invasion and infarction.	Diagnostic endoscopy, Contrast-enhanced CT Scan, MRI (preferred)	Same as Stage 3

Figure 1: Proposed staging of rhino-orbito-cerebral mucormycosis with clinical symptoms and signs, evaluation and diagnosis.

leading to poor outcomes. Amphotericin B is the drug of choice in a case of Mucormycosis. A study shows that serum albumin attenuates the toxicity of Amphotericin B at a membrane level by affecting its aggregation state.[12] In this way, serum albumin in blood may balance deleterious effects of the drug mediated by serum low-density lipoproteins. Hence, the presence of hypoalbuminemia in patients with ROCM can exert poor prognosis, especially where surgical intervention is indicated.

Reports of COVID-19-associated mucormycosis have been increasing in frequency since early 2021, particularly among patients with uncontrolled diabetes. Patients with diabetes and hyperglycemia often have an inflammatory state that could be potentiated by the activation of antiviral immunity to SARS-CoV2, which might favor secondary infections. In this review, we analyzed 80 published and unpublished cases of COVID-19-associated mucormycosis. Uncontrolled diabetes, as well as systemic

corticosteroid treatment, was present in most patients with COVID-19-associated mucormycosis, and ROCM was the most frequent disease. Mortality was high at 49%, which was particularly due to patients with pulmonary or disseminated mucormycosis or cerebral involvement. Furthermore, a substantial proportion of patients who survived had life-changing morbidities (e.g., loss of vision in 46% of survivors). One study showed that COVID-19-associated mucormycosis is associated with high morbidity and mortality. Furthermore, diagnosis of pulmonary mucormycosis is particularly challenging and might be frequently missed in India.[13]

Figure 1 Shows the proposed staging of ROCM and the important parameters. ROCM is divided into 4 stages according to severity, depending on clinical symptoms, signs, provisional and confirmatory assessments. The primary diagnostic modalities used are diagnostic nasal endoscopy, Contrast Enhanced Magnetic Resonance Imaging or Computed tomography, culture and melecular diagnosis of coolected tissue sample and hystopathology with special stains.

Our study has shown that hypoalbuminemia is associated with ROCM. However, even though the incidence of severe hypoalbuminemia increases in severe ROCM, severity of hypoalbuminemia is not significantly correlated with the disease severity. Hence, the presence of hypoalbuminemia can be used as a predictor of severe ROCM, but severity of hypoalbuminemia may not be proportionally correlated to ROCM severity; hence, hypoalbuminemia severity cannot be used as a factor of ROCM severity.

Limitations of the study

As mucormycosis is a rare fungal disease, with the prevalence being 0.14 cases per 1000 population in India, we could enlist o nly 41 sample cases.

CONCLUSION

This study was a hospital-based prospective cross-sectional study done on 41 ROCM patients to look for any relationship between two factors, occurrence of hypoalbuminemia and stage of ROCM. In our study population, Stage 3 ROCM was most common (42%). Total 85% of the ROCM patients developed hypoalbuminemia, among them 51% developed milder variety and the 34% developed the severe type of hypoalbuminemia. According to the data analysis, it is found out that hypoalbuminemia is associated with ROCM. However, even though the incidence of severe hypoalbuminemia increases in severe ROCM, severity of hypoalbuminemia is not significantly correlated with the disease severity. Hence, the presence of hypoalbuminemia can be used as a predictor of severe ROCM, but severity of hypoalbuminemia may not be proportionally correlated to ROCM severity; hence, hypoalbuminemia severity cannot be used as a factor of ROCM severity.

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REFERENCES

1. Available from: https://www.cdc.gov/fungal/diseases/mucormycosis/index.html
2. Ravani SA, Agrawal GA, Leuva PA, Modi PH and Amin KD. Rise of the phoenix: Mucormycosis in COVID 19 times. Indian J Ophthalmol. 2021;69(6):1563-1568.
   https://doi.org/10.4103/ijo.IJO_310_21
3. Sen M, Lahane S, Lahane TP, Parekh R and Honavar SG. Mucor in a viral land: A tale of two pathogens. Indian J Ophthalmol. 2021;69(2):244-252.
   https://doi.org/10.4103/ijo.IJO_3774_20
4. Sarkar S, Gokhale T, Choudhury SS and Deb AK. COVID-19 and orbital mucormycosis. Indian J Ophthalmol. 2021;69(4):1002-1004.
   https://doi.org/10.4103/ijo.IJO_3763_20
5. Sen M, Honavar SG, Sharma N and Sachdev MS. COVID-19 and Eye: A review of ophthalmic manifestations of COVID-19. Indian J Ophthalmol. 2021;69(3):488-509.
   https://doi.org/10.4103/ijo.IJO_297_21
6. Rao R, Shetty AP and Nagesh CP. Orbital infarction syndrome secondary to rhino-orbital mucormycosis in a case of COVID-19: Clinico-radiological features. Indian J Ophthalmol. 2019;69(6):1627-1630.
   https://doi.org/10.4103/ijo.IJO_1053_21
7. Cornely OA, Alastruey-Izquierdo A, Arenz D, Chen SC, Dannaoui E, Hochhegger B, et al. Global guideline for the diagnosis and management of mucormycosis: An initiative of the European confederation of medical mycology in cooperation with the mycoses study group education and research consortium. Lancet Infect Dis. 2019;19(12):e405-e421.
   https://doi.org/10.1016/S1473-3099(19)30312-3
8. Skied A, Pavleas I and Drogari-Apiranthitou M. Epidemiology and diagnosis of mucormycosis: An Update. J Fungi (Basel). 2020;6(4):265.
   https://doi.org/10.3390/jof6040265
9. Available from: https://www.thehindu.com/news/national/mucormycosis-not-uncommon-in-india-studies/article34617210.ece last accessed on 15/09/2022.
10. Sunghye K, McClave SA, Martindale RG, Miller KR and Hurt RT. Hypoalbuminemia and clinical outcomes: What is the mechanism behind the relationship? Am Surg. 2017;83(11):1220-1227.
    https://doi.org/10.1177/000313481708301123
11. Moman RN, Gupta N and Varacallo M. Physiology, Albumin. Vol. 119. Treasure Island (FL). StatPearls Publishing; 2022. p. 434.

12. Aeamwit P, Yu BG, Lavasanifar A, Samuel J and Kwon GS. The effect of serum albumin on the aggregation state and toxicity of amphotericin B. J Pharm Sci. 2000;89(12):1589-1593.
https://doi.org/10.1002/1520-6017(200012)89:12<1589:aid-jps10>3.0.co;2-6

13. Martin H, Seidel D, Criscuolo M, Dargenio M, Rácil Z, Piedimonte M, et al. The emergence of COVID-19 associated mucormycosis: A review of cases from 18 countries. Lancet Microbe. 2022;3(7):e543-e552.
https://doi.org/10.1016/S2666-5247(21)00237-8

Authors Contribution:
SM- Concept and design the study, approved final draft of manuscript; **SD-** Reviewed literature, collected data, statistical analysis and interpretation, preparation of manuscript, and revision of manuscript; **AC-** reviewed final manuscript, concept, and coordination; **MM-**Provision of medical data; and SRS-Provision of surgical data.

Work attributed to:
Bankura Sammilani Medical College and Hospital, Bankura - 722 102, West Bengal, India.

Orcid ID:
Dr. Souvik Das - https://orcid.org/0000-0001-8268-9929
Dr. Shyamash Mandal - https://orcid.org/0000-0002-2543-7466
Dr. Atanu Chandra - https://orcid.org/0000-0002-3809-8926
Dr. Monoj Mukherjee - https://orcid.org/0000-0002-9865-455X

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