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Original Article

Diabetes, COVID 19 and mucormycosis: Clinical spectrum and outcome in a tertiary care medical center in Western India

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ABSTRACT

Aims: Diabetes Mellitus predisposes patients to invasive fungal infections. There has been a recent surge of Mucormycosis with COVID 19 infection particularly in patients with diabetes. This study aims to study the clinical spectrum of CAM (COVID -associated Mucormycosis) with diabetes and subsequent outcomes.

Material and methods: This was a descriptive study conducted at a single COVID Care Centre in India in patients with COVID Associated Mucormycosis from April 12, 2021 to May 31, 2021.

Results: Among 953 hospitalized patients with COVID 19 infection, 32 patients had CAM with an incidence of 3.36%. In patients with CAM, 87.5% had Diabetes Mellitus as the most common co-morbidity. The majority of the patients had poor glycemic control with a mean HbA1c of 9.06%. Out of the total study population, 93% had prior exposure to high dose corticosteroids. During the study period, 12.5% patients of CAM did not survive.

Conclusion: Mucormycosis is an angioinvasive fungal infection with high mortality. The disease has surged in COVID 19 pandemic due to uncontrolled diabetes and improper corticosteroid use.

1. Introduction

The Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) virus has caused a global pandemic of Coronavirus (COVID-19) disease. There are more than 170 million confirmed COVID-19 cases worldwide with over 3.5 million deaths as of May 2021 [1]. There has been reports of increased incidence of fungal infections in patients with COVID-19. There were earlier reports of COVID associated Pulmonary Aspergillosis (CAPA) and candidemia [2,3]. However, recently there has been sudden surge in cases of Mucormycosis in patients with COVID-19 [4].

Mucormycosis is a formidable angioinvasive opportunistic infection in an immunocompromised host. The spectrum of mucormycosis involves rhino-orbital-cerebral, pulmonary, disseminated, cutaneous, gastrointestinal and disseminated form of disease. The major risk factors for the disease are diabetes, neutropenia, iron overload, malignancy and organ transplant [5].

Diabetes is the most common metabolic disorder and is an independent risk factor for Severe COVID-19 and Mucormycosis. In patients with diabetes affected with COVID-19 superinfection with Mucormycosis will lead to adverse clinical outcome and prolonged hospital stay. This study aims to study the clinical spectrum of Mucormycosis in patients with COVID-19 and diabetes and their subsequent outcomes.

2. Material and Methods

2.1. Study setting

This descriptive study was conducted at a COVID Care Centre in Western India from Apr 12, 2021 to May 31, 2021. All laboratory-confirmed COVID-19 cases by RTPCR (Real Time Reverse Transcription Polymerse Chain Reaction) nasopharyngeal & throat swab were admitted at this centre. Severe COVID-19 infection was defined by Sp02 < 90% or Respiratory rate >30/min at admission or

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during hospital stay. Post COVID 19 cases were defined who had either clinical recovery from respiratory symptoms or had passed 28 days since the onset of symptoms of COVID 19. Lymphocytopenia was defined by absolute lymphocyte count<1000/mm^3.

Mucormycosis was defined by clinico-radiological suspicion with visualisation of broad branched aseptate fungal hyphae on KOH mount direct microscopy and histopathology specimen by fungal stains or isolation of zygomycetes on fungal culture. Written informed consent was taken from patients or nearest of kin. This study was approved by Institutional Ethics Committee.

2.2. Statistical analysis

Data was compiled in MS Excel and analysed using SPSS ver 20.0. Descriptive statistics were presented as mean and standard deviation for quantitative variables and as frequencies with percentages for qualitative data. Associations between variables were explored for hypothesis generation using Chi square test for qualitative variables and correlation or unpaired *t*-test for quantitative variables.

2.3. Results

2.3.1. Demography

During the study period, 953 patients were hospitalized with COVID-19 infection, out of them 32 (3.36%) patients had CAM (COVID-Associated Mucormycosis). The mean age of patients was 58.28 (±8.57) yrs. In 32 patients with CAM, 17/32 (53.1%) were males and the rest were females. All the patients were admitted in a dedicated COVID Care Centre (see Table 1).

2.3.2. Risk factors

In patients with CAM, 28/32 (87.5%) had diabetes as the most frequent co-morbidity. In patient with diabetes, mean blood glucose was 242.63 (±84.81) g/dl with mean glycated haemoglobin (HbA1c) of 9.06% (±2.19) at admission. There were no patients with diabetic ketoacidosis in our study. The majority of the patients, 30/32 (93%) had history of steroid exposure in form of either dexamethasone and methylprednisolone. The duration and amount of exposure could not be determined as it varied due to physician preference and intake of OTC (over the counter) steroid by the patients. None of our patients received anti- IL6 therapy or monoclonal antibodies. There were no cases of malignancy, organ transplant or HIV/AIDS with Mucormycosis in our study.

2.3.3. Clinical presentation

In Patients with CAM 30/32 (93.8%) had headache, 20/32 (62.5%) had nasal symptoms in form of rhinorrhoea & nasal stuffiness and 19/32 (59.4%) had eyes symptoms in form of redness or eye pain. On admission, 18/32 (56.2%) patients had history or presented with Severe COVID-19 pneumonia. At the time of diagnosis of CAM, 22/32 (68.8%) had hypoxemia and required supplemental oxygen. The mean duration from onset of COVID-19 to diagnosis of CAM was 17.28 (±11.76) days. In patients with CAM, none of them were fully vaccinated against COVID-19. Two patients had received a single dose of ChAdOx1- Oxford–AstraZeneca (Covishield) COVID-19 vaccine. Both the patients are still admitted at our centre and are on antifungal therapy.

2.3.4. Laboratory evaluation & diagnosis

At admission, 17/32 (53.3%) patients with CAM had a mean leucocyte count: 11478.13 (±3693.83)/mm^3. Leucocytosis was significantly higher in non-survivors with mean leucocyte count of 15775.0 (±7650.4) (see Fig. 1).

At admission, 24/32 (75%) patients had lymphocyte count 954.04 (±769.89)/mm^3. Contrast Enhanced Commuted Tomography/MRI Paranasal Sinuses revealed 19/32 (59.4%) with orbital involvement. (see Fig. 3 Among the Paranasal sinuses, Maxillary and Ethmoid sinus were predominantly involved in 28/32 (87.5%) cases. We had one patient with Cavernous sinus thrombosis with ophthalmoplegia and one patient with cutaneous mucormycosis. (see Fig. 2) There were no patients with cerebral, pulmonary or disseminated mucormycosis.

The diagnosis of Mucormycosis was confirmed with microscopy 29/32 (90.6%),histopathology 27/32 (84.3%) and by culture in 27/32 (34.7%) cases (see Fig. 4).

2.3.5. Treatment and outcome

Patients at our centre were started on liposomal amphotericin B with glycemic control on clinical suspicion of Mucormycosis followed by endoscopic debridement. In 30/32 (93.3%) patients, endoscopic debridement of sinuses was done. One patient died before surgery while another denied surgery. During the entire duration of study 4/32 (12.5%) patients did not survive, 5 (15.6%) were discharged and the rest are in hospital on parenteral antifungals.

3. Discussion

India has the highest global burden of Mucormycosis. The prevalence of Mucormycosis in India is 140 per million of population based on a computational model [6]. The annual incidence has been around 129 cases/year from India (2013–2015) [7]. In a recent publication, 187 cases of CAM in India were reported, with incidence was 0.27% among hospitalized cases during the study period from September to December 2020. The caseload of Mucormycosis had increased by 2.1 folds from the previous year [8]. Currently, 14,872 cases of CAM have been notified in India as of May 28, 2021 [4].

Our study had an incidence of 3.36% CAM in hospitalized patients of COVID-19 during the study period. The present surge in Mucormycosis cases is possibly due to the high burden COVID-19 in the country.

The mean duration of onset of Mucormycosis was 17.28 (±11.36) days after the onset of COVID-19. The majority of patients, 21/32 (65.6%) patients of CAM, were in post COVID syndrome (PCS), after clinical recovery from COVID-19. The median incubation period of Mucormycosis is not known and is considered to be 7–10 days after percutaneous exposure [9]. Hence, exposure of Mucormycosis during hospitalization or Healthcare Associated Mucormycosis requires consideration [10].

Diabetes is the most frequent co-morbidity in Mucormycosis in about 73.5% in India [11]. However, in western countries diabetes is associated with 17% cases of Mucormycosis [12] Incidence of Mucormycosis is around 1.6 cases/1000 patients with diabetes [13]. Diabetes was associated in our study with 28/32 (87.5%) cases of CAM, with poor glycaemic control, in form mean blood glucose of 242.63 (±84.81) g/dl & mean glycated haemoglobin (HbA1c) of 9.06% (±2.19) at admission.

In our patients, 17/32 (53.3%) had neutrophilic leucocytosis with mean leucocyte count: 11478.13 (±3693.83)/mm3. This pattern of leucocytosis is similar to Mucormycosis in patient without malignancy [14]. Lymphocytopenia is frequently associated with COVID-19 and may correlate to its severity [15]. We had 24/32 (75%) patients with lymphocytopenia with mean lymphocyte count 954.04 (±769.89)/mm^3. However, the relationship between lymphocytopenia and CAM requires further evaluation.

The radiological pattern of CAM was predominantly Rhino-orbital 19/32 (59.4%), while others had Sinonasal Mucormycosis. The pattern of involvement is similar to previous reports with the

Table 1
Characteristics in study population and among survivors and non-survivors.

Parameter		Overall (n = 32)	Survivors (n = 28)	Non-Survivors (n = 4)	P value
Age (yrs)		58.28 (±8.57)	58.46 (±9.08)	57.00 (±3.92)	0.588
Sex-no.(%)	Female	17 (53.1)	14 (82.4)	3 (17.6)	0.349
	Male	15 (46.9)	14 (93.3)	1 (6.7)	
Comorbidity-no.(%)					
Diabetes Mellitus		28 (87.5)	26 (92.9)	6 (7.1)	0.015
Hypertension		16 (50)	14 (87.5)	2 (12.5)	0.999
Coronary Artery disease		2 (6.3)	1 (50.0)	1 (50.0)	0.098
COVID 19 Severity- no.(%)	Non-Severe	14 (43.8)	14 (100)	0 (0)	0.169
	Severe	18 (56.2)	14 (77.8)	4 (22.2)	
Hypoxemia at Mucor diagnosis-no.(%)		22 (68.8)	18 (81.8)	4 (8.2)	0.149
Mean Duration from onset of COVID 19 to Mucor diagnosis-(days)		17.28 (±11.36)	17.93 (±11.76)	12.75 (±8.32)	0.403
Mucor Diagnosis no.(%)	Active COVID 19	11 (34.4)	8 (72.7)	3 (27.3)	0.067
	Post COVID 19	21 (65.6)	20 (95.2)	1 (4.8)	
History of Corticosteroid usage- no.(%)	No	2 (6.3)	2 (100)	0 (0)	0.581
	Yes	30 (93.7)	26 (86.7)	4 (13.3)	
CLINICAL					
Symptoms- no.(%)					
Headache		30 (93.8)	27 (90.0)	3 (10.0)	0.638
Nasal symptoms		20 (62.5)	19 (95.0)	1 (5.0)	0.098
Eye symptoms		19 (59.4)	15 (78.9)	4 (21.1)	0.077
Palatal discoloration		3 (9.4)	3 (100)		
Cutaneous symptoms		1 (3.1)	1 (100)		
LABORATORY INVESTIGATIONS					
Parameters-Mean ± SD					
Hemoglobin (g/dl)		11.41 (±2.17)	11.39 (±2.26)	11.50 (±1.73)	0.931
Total Leucocyte Count (per mm^3)		11478.13 (±3693.83)	10864.3 (±2456.9)	15775.0 (±7650.4)	**0.010**
Absolute Lymphocyte Count		954.04 (±769.89)	819.75 (±513.14)	1492.33 (±1934.6)	0.119
Platelets ($10^5/mm^3$)		2.66 (±0.94)	2.76 (±0.93)	2.00 (±0.82)	0.134
Serum Bilirubin		0.76 (±0.35)	0.73 (±0.33)	1.03 (±0.57)	
Alanine Aminotransferase (IU/L)		59.81 (±64.05)	58.32 (±69.61)	68.00 (±12.99)	0.556
Serum Creatinine (mg/dl)		1.20 (±0.63)	1.12 (±0.55)	1.75 (±0.96)	0.063
Internal Normalized Ratio (INR)		1.18 (±0.21)	1.17 (±0.14)	1.25 (±0.50)	0.502
HbA1c		9.06 (±2.19)	9.15 (±2.06)	8.50 (±3.32)	0.590
Blood Glucose at admission (mg/dl)		242.63 (±84.81)	233.86 (±72.37)	304.00 (±146.51)	0.412
RADIOLOGICAL					
Radiological Involvement of Paranasal Sinus/Orbit- no.(%)					
Maxillary Sinus		28 (87.5)	25 (89.3)	3 (10.7)	0.419
Ethmoid Sinus		28 (87.5)	25 (89.3)	3 (10.7)	0.419
Sphenoid Sinus		20 (62.5)	16 (80.0)	4 (20.0)	0.098
Frontal Sinus		12 (37.5)	12 (100)	0 (0)	0.098
Orbit		19 (59.4)	15 (78.9)	4 (21.1)	0.077
MICROBIOLOGICAL					
Microscopy Positive-no.(%)		29 (90.6)	25 (89.2)	4 (100)	<0.001
Histopathological Diagnosis-no.(%)		27 (84.37)	26 (92.8)	2 (50)	<0.001
Culture Growth-no-(%)		14 (34.7)	13 (46.4)	1 (25)	<0.001
SURGICAL INTERVENTION					
Endoscopic Debridement-no.(%)		30 (93.8)	27 (90)	3 (10)	0.098

predominant risk factor in the form of diabetes [16].

In our study 4/32 (12.5%) patients did not survive in the study period of seven weeks.

The reported mortality of Rhinocerebral Mucormycosis in patients with diabetes is 40–50% [16]. Prognosis is improved in cases of Sinonasal disease with early surgical debridement and mortality has been reported to be less than 10% [17]. The mortality appears to be less in our case possibly due to early diagnosis with early surgical debridement. However, we did not have any patients with cerebral or disseminated Mucormycosis disease. Moreover, we did not have any patients with hematological malignancy or organ transplant. Still, the majority of 23/32 (71.8%) of patients are admitted and the final outcome at 12 and 24 weeks needs to be assessed.

There are numerous reasons for the emergence of Mucormycosis in COVID 19. In our study diabetes was the most common comorbidity. Diabetes mellitus and COVID-19 share a bidirectional relationship with adverse outcomes. Diabetes is a proinflammatory state which leads to deficient control of SARS-CoV-2 replication and severe COVID 19 infections [18]. SARS-CoV-2 infection leads to decreased insulin secretion due to direct pathogenic effect on pancreatic islet cells. It also induces insulin resistance due to transient hyper-inflammatory state [19]. Subsequently, a state of hyperglycemia is produced leading to the growth of invasive mucormycosis.

Corticosteroids are considered essential therapy in patients with COVID 19 on supplemental oxygen [20]. Though traditionally, usage of prednisolone or equivalent 1 mg/kg for 3 weeks or more is considered a risk factor for Mucormycosis [21], certain case reports have shown occurrence of Mucormycosis after a short course of steroids [22]. The effect of corticosteroids in CAM is multifaceted. First, they can lead to immunosuppression since they impair migration, phagocytosis and phagolysosome formation in the macrophages. Secondly, they lead to drug induced hyperglycemia and worsening of glycemic control in patients with diabetes. Moreover, in countries like India where it is available as OTC drugs, improper and prolonged steroid use could lead to increase susceptibility to Mucormycosis [23].

SARS-CoV-2 infects immune cells (CD3, CD4, and CD8 T cells)

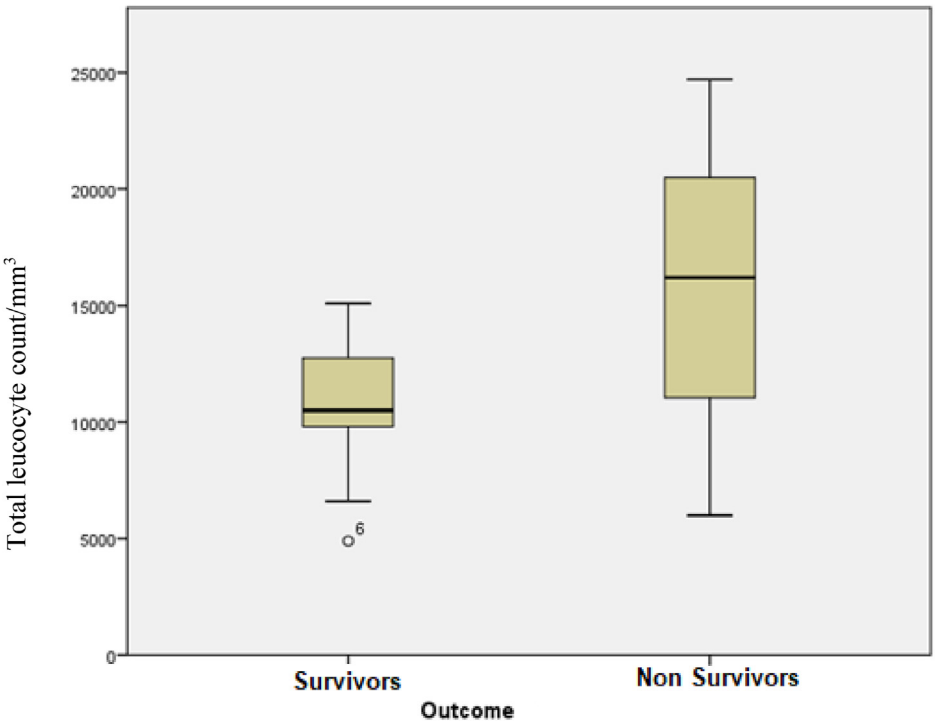

Fig. 1. Box and whisker plot showing relationship of total leucocyte count with outcome in patients with Covid-Associated Mucormycosis.

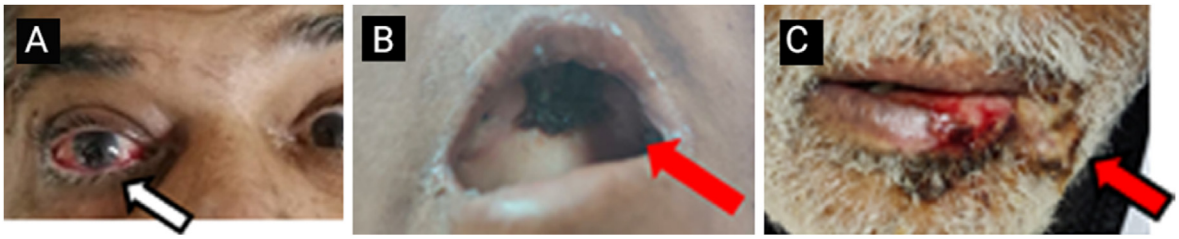

Fig. 2. Clinical spectrum of Covid -Associated Mucormycosis **(A)** Right Orbital cellulitis (B) Palatal Mucormycosis **(C)** Cutaneous Mucormycosis involving face in our patients.

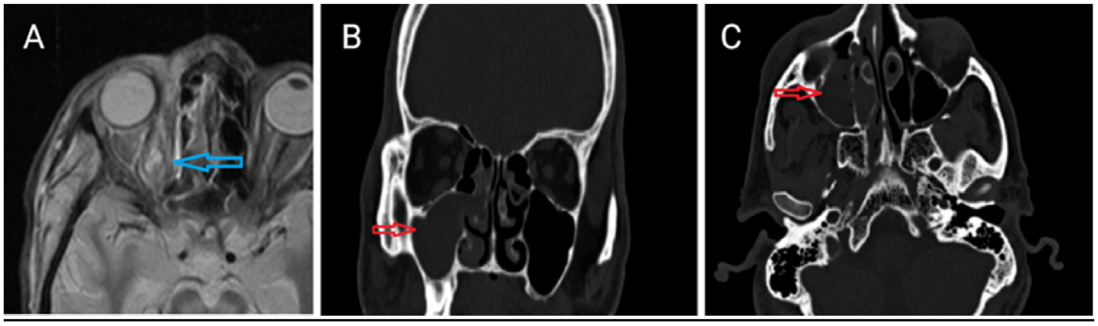

Fig. 3. Radiological images of Rhino-orbital Mucormycosis (A) MRI Orbit suggestive of right orbital involvement. (B&C) Commuted Tomography of Paranasal sinuses suggestive of right maxillary sinusitis.

leading to apoptosis of lymphocytes. The resultant lymphocytopenia causes deficient innate immunity causing immune dysregulation and a cytokine storm [24]. Diabetes mellitus affects the adaptive immune system by inhibition of neutrophil chemotaxis, phagocytosis, and intracellular killing of pathogens [24]. Thus, SARS-CoV-2 infection in a patient with diabetes leads to a state of immune dysregulation. Compounding to this state, the usage of steroids causes immunosuppression. Overall, COVID-19, Diabetes and corticosteroid usage leads to high risk for invasive fungal Mucormycosis.

SARS-CoV-2 infection causes endothelial dysfunction due to direct viral invasion and host inflammatory response causing apoptosis and pyroptosis of endothelial cells [24]. Diabetes is a chronic inflammatory state associated with endothelial dysfunction

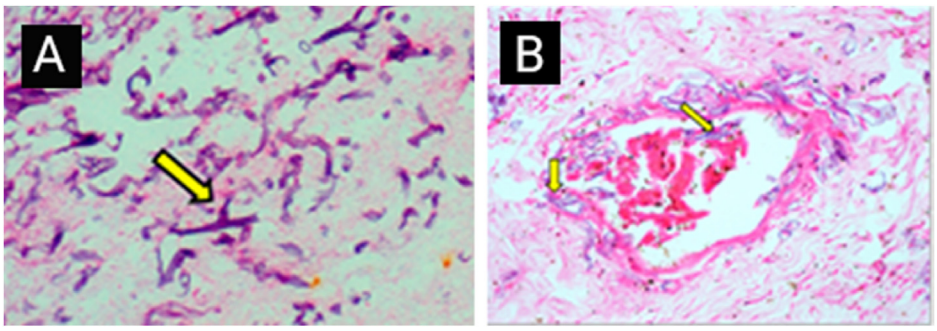

Fig. 4. Histopathology of post-operation specimen with Hematoxylin &Eosin staining showing(**A**) Broad branched aseptate fungal hyphae suggestive of Mucormycosis (**B**) Fungal invasion into the vessel wall.

[25]. Endothelial adhesion and angioinvasion are critical for invasion of Mucorales [5]. Thus, patients with diabetes with COVID-19 infection are at high risk for invasive Mucormycosis.

Overall, hyperglycemia in patients with diabetes and COVID-19 on steroids contributes to risk of Mucormycosis by following mechanism: a) Induction of defect in neutrophil-macrophage phacytocytic system; b) Upregulation and increased expression of GRP78 receptor in humans and mucorales specific protein CotH; c) Hyperglycation of iron sequestering proteins leading to disruption in iron sequestration and increased delivering of iron to Mucorales [5].

India has high burden of Mucormycosis among patients with COVID-19 in the world [7]. The incidence has sharply risen during the second wave of COVID-19 with over 14,872 cases of mucormycosis till date [4]. The second wave of COVID 19 has been attributed to B.1.617 variant of SARS-CoV-2, also being called a 'double mutant' or the 'delta' variant [26]. The B.1.617 variant of SARS-CoV-2 is considered more infections with increased virulence. The effect of B1.617 variant on increased risk of Mucormycosis requires further consideration and research.

Our study has notable limitations. It is a single centre study with limited cases of Mucormycosis and may not represent the full picture of the current state of the world. Moreover, we explored attributability of diabetes and COVID19 in the risk of Mucormycosis and did not have enough data for other risk factors like malignancy, neutropenia, HIV or organ transplant. We did not have a control group of patients without COVID-19 with Mucormycosis. Moreover, we do not have outcomes of CAM at 12 or 24 weeks and attributability of mortality. However, our study provides useful insights for demographic and clinical profile of CAM and its relation with diabetes.

4. Conclusion

Mucormycosis is angioinvasive fungal disease with significant morbidity and mortality. The disease has risen dramatically due to interplay of COVID 19 pandemic, uncontrolled diabetes and inappropriate corticosteroid use leading to pathogenic invasion and adverse outcomes. The treatment involves early detection, surgical debridement and antifungal drugs for better survival.

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Declaration of competing interest

The Authors declare there is no conflict of interest.

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