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ORIGINAL ARTICLE

COVID-19-associated subacute invasive pulmonary aspergillosis

Satish Swain[1] | Animesh Ray[1] | Radhika Sarda[1] | Surabhi Vyas[2] | Gagandeep Singh[3] | Pankaj Jorwal[1] | Parul Kodan[1] | Puneet Khanna[4] | Immaculata Xess[3] | Sanjeev Sinha[1] | Naveet Wig[1] | Anjan Trikha[4]

[1]Department of Medicine, All India Institute of Medical Sciences, New Delhi, India

[2]Department of Radiology, All India Institute of Medical Sciences, New Delhi, India

[3]Department of Microbiology, All India Institute of Medical Sciences, New Delhi, India

[4]Department of Anaesthesia and Critical Care, All India institute of Medical Sciences, New Delhi, India

Correspondence
Dr Animesh Ray, Department of Medicine, All India institute of medical Sciences, New Delhi, India.
Email: doctoranimeshray@gmail.com

Abstract

Background: Though invasive pulmonary aspergillosis is a well known complication of COVID-19 pneumonia, indolent forms of aspergillosis have been rarely described.

Methods: We prospectively collected the clinico-radio-microbiological data of 10 patients of subacute invasive pulmonary aspergillosis (SAIA), who presented to our hospital with recent history of COVID-19 pneumonia along with cavitary lung disease, positive IgG (against *Aspergillus*) with or without positive respiratory samples for *Aspergillus spp*.

Result: The mean age of presentation of SAIA was 50.7 ± 11.8 years. All the patients had recently recovered from severe COVID-19 illness with a mean duration of 29.2 ± 12 days from COVID-19 positivity. Cough was the predominant symptom seen in 8/10 (80%) patients followed by haemoptysis. 7/10 (70%) patients were known diabetic. While serum galactomannan was positive in 5/9 patients (55.5%), fungal culture was positive in 2/7 patients (28.5%) and polymerase chain reaction (PCR) for *Aspergillus* was positive in three patients. Eight (80%) patients presented with a single cavitary lesion; pseudoaneurysm of pulmonary artery was seen in two patients and post-COVID-19 changes were seen in all patients. All patients were treated with voriconazole, out of which four (40%) patients died during the follow-up period.

Conclusion: SAIA should be considered in the differential diagnosis of cavitating lung lesions in patients with recent history of COVID-19 in the background of steroid use with or without pre-existing diabetes.

KEYWORDS
COVID-19, fungal infection, steroid, subacute invasive pulmonary aspergillosis

1 | INTRODUCTION

COVID-19 has been associated with a number of complications in the acute setting like severe COVID-19 pneumonia, acute respiratory distress syndrome (ARDS), pneumothorax and pulmonary thromboembolism. It has also been linked, though uncommonly, to secondary infections like bacterial pneumonia, bacteraemia[1] and pulmonary fungal infections. Within pulmonary fungal infections, COVID-19-associated pulmonary aspergillosis (CAPA)[2] and pulmonary mucormycosis have been reported as complications of COVID-19. However, subacute invasive pulmonary aspergillosis (SAIA) has not been highlighted in this group of patients. Herein, we

Satish Swain and Animesh Ray has equally contributed to the manuscript (shared first authorship).

TABLE 1 Clino-radio-microbiological profile and outcome of SAIA patient cohort

	Patient #1	Patient #2	Patient #3	Patient #4
Age (years)	60	64	43	31
Gender	Female	Male	Male	Male
Medical History	DM	DM	None	DM
HbA1c	9.0	6.07	6.68	9.6
Post-COVID-19 severity	Severe	Severe	Severe	Severe
Steroid intake	Yes	Yes	Yes	Yes
Time from COVID-19 positivity to diagnosis of SAIA (in days)	30	21	32	50
Presenting complains	Cough	Cough Sob Fever	Cough Haemoptysis	Cough Sob
Anti-fungal therapy	Voriconazole	Voriconazole	Voriconazole	Voriconazole
Outcome (day 28 from diagnosis)	Improving; Discharged on oxygen 4 L/min	Cough and sob persisting Hospitalised On oxygen 6L/min	Improving Discharged on room air	Improving Discharged on room air
Outcome (day 90 from diagnosis)	Cough improved; Currently on 2 L/min oxygen	Died (time of death after developing COVID-19 = 42 days)	Improved (mild intermittent dry cough)	Improving (no sob; mild intermittent dry cough)
Fungal KOH (respiratory sample)	Sputum: hyaline septate hyphae	No fungal elements	No fungal elements	Sputum: aseptate + Septate hyphae
Fungal Culture[b]	Negative	Sputum: *Aspergillus fumigatus*	Negative	Sputum: *Aspergillus fumigatus*
Fungal BAL PCR[c]	NA	BAL *Aspergillus fumigatus*	NA	NA
BAL-GM	NA	2.257	NA	NA
Serum IgG Aspergillus	14.67	52.5	109.26	178.9
Serum GM[a]	1.01	2.8	0.311	>8.0
Evidence for tuberculosis (sputum gene Xpert/AFB)	Negative	Negative	Negative	Negative
CT chest Imaging Cavity: 1. Number- 2. Site- 3. Size-	1. Single 2. Lt. LL 3. 0.4 × 0.7 cm	1. Single 2. Lt. LL 3. 1 × 1 cm	1. Single 2. Rt. LL 3.1.1 × 2 cm	1. Two 2. Lt. UL LL 3. 3 × 2.5 cm, 2 × 1.5 cm
CT chest Imaging Background:	GGOs Septal thickening	GGOs, Septal Thickening, Consolidation	GGOs, Septal Thickening, Fibrotic bands	GGOs, Septal Thickening
CT chest Imaging (other findings)	None	None	Pseudoaneurysm of PA 2.2 × 2.2 cm in Rt. LL	Thrombus in Lt. Lobar branch of PA Air crescent sign
Follow-up CT scan	N/A		N/A	Decrease in cavity size and scarring of cavity

Abbreviations: AFB: Acid-fast bacilli B/L: Bilateral; BAL: Broncho-alveolar lavage; CAD: Coronary Artery Disease; CT: computed tomography; DLBCL: Diffuse large B cell lymphoma; DM: Diabetes Mellitus; GGOs: Ground glass opacity; HTN: Hypertension; LL: Lower Lobe; Lt.: Left; N/A: Not available; PA: Pulmonary Artery; Rt.: Right; Sob: Shortness of breath.

[a]Serum GM was sent for 9 patients.

[b]Fungal cultures of respiratory samples were done 7 patients.

[c]BAL was done in 3 patients.

Patient #5	Patient #6	Patient #7	Patient #8	Patient #9	Patient#10
52	70	47	55	40	45
Female	Female	Male	Male	Male	Female
DM HTN	DM HTN	DM CAD	DM	DLBCL	None
7.77	8.76	12.8	9.61	NA	6.01
Severe	Severe	Severe	Severe	Severe	Severe
Yes	Yes	Yes	Yes	Yes	Yes
34	22	19	25	15	45
Cough Haemoptysis	Sob	Cough Haemoptysis	Cough Haemoptysis	Cough Sob	Sob
Voriconazole	Voriconazole	Voriconazole	Voriconazole	Voriconazole	Voriconazole
Died (time of death after developing COVID-19 = 49 days)	Died (time of death after developing COVID-19 = 42 days)	Improving Discharged on room air	Improving Discharged on room air	Died (time of death after developing COVID-19 = 19 days)	Improving Discharged on O2 3L/min
		Improved	Improved		Improving; Currently on 1.5L/min oxygen
No fungal elements	NA	No fungal elements	BAL: hyaline septate hyphae	NA	NA
Negative	NA	Negative	Negative	NA	NA
NA	NA	BAL: *Aspergillus fumigatus*	BAL: *Aspergillus fumigatus*	NA	NA
NA	NA	0.84	0.83	NA	NA
196.95	139.27	19.97	25.71	20.68	30.90
0.6	1.09	0.84	0.13	NA	1.60
Negative	N/A	Negative	Negative	Negative	N/A
1. Single 2. Rt. LL 3. 3.9 × 2.4 cm	1. Single 2. Rt. LL 3. 1 × 1 cm	1. Single 2. Lt. LL 3. 11 × 6.5 cm	1. Single 2. Rt. LL 3. 2.6 × 1.7 cm	1. Multiple 2. B/L 3. 4.5 × 4 cm	1. Single 2. Lt. LL 3. 1.2 × 1 cm
GGOs, Septal Thickening, Fibrosis	GGOs, Septal Thickening, Fibrosis	GGOs, Septal Thickening, Fibrosis	GGOs	GGOs, Septal Thickening	GGOs Septal Thickening
Pseudoaneurysm of basal segment	pulmonary arterial hypertension	Filling defect in all branches of PA	Rt. Pleural effusion	None	Pneumo-mediastinum
—	—	N/A	N/A	N/A	Decrease in cavity size (1 × 0.9 cm) and wall thickness.

TABLE 2 Diagnostic feature of SAIA in the study cohort

Clinico-epidemiological profile	
Mean age	50.7 ± 11.8 years
Sex	Male:Female = 6:4
Medical comorbidities	Diabetes 7/10 (70%) -mean HbA1c of 8.5 ± 2.1% Hypertension 3/10 (30%) Malignancy 1/10 (10%)
Symptoms	Cough 8/10 (80%) Shortness of Breath 5/10 (50%) Haemoptysis 4/10 (40%)
Mean duration from COVID-19 positivity to diagnosis of SAIA (in days)	29.2 ± 12 days
Microbiological profile	
Aspergillus Serum IgG Ab	10/10 (100%)
Serum GM	5/9 (55.5%)[a]
Aspergillus from fungal culture of respiratory specimens	2/7 (28.57)[b]
Aspergillus PCR in BAL	3/3 (100%)[c]
Radiological profile	
Cavity	Single 8/10(80%) Multiple 2/10(20%)
Post-COVID-19 changes	10/10(100%)
Other CT findings	Pseudoaneurysm of PA 2/10 (20%) PA thrombus 2/10(20%) Pneumo-mediastinum 1/10 (10%) Pulmonary arterial hypertension 1/10 (10%) Pleural effusion 1/10 (10%)

Abbreviation: PA, Pulmonary Artery.

[a]Serum GM was sent for 9 patients.

[b]Fungal cultures of respiratory samples were done 7 patients.

[c]BAL was done in 3 patients.

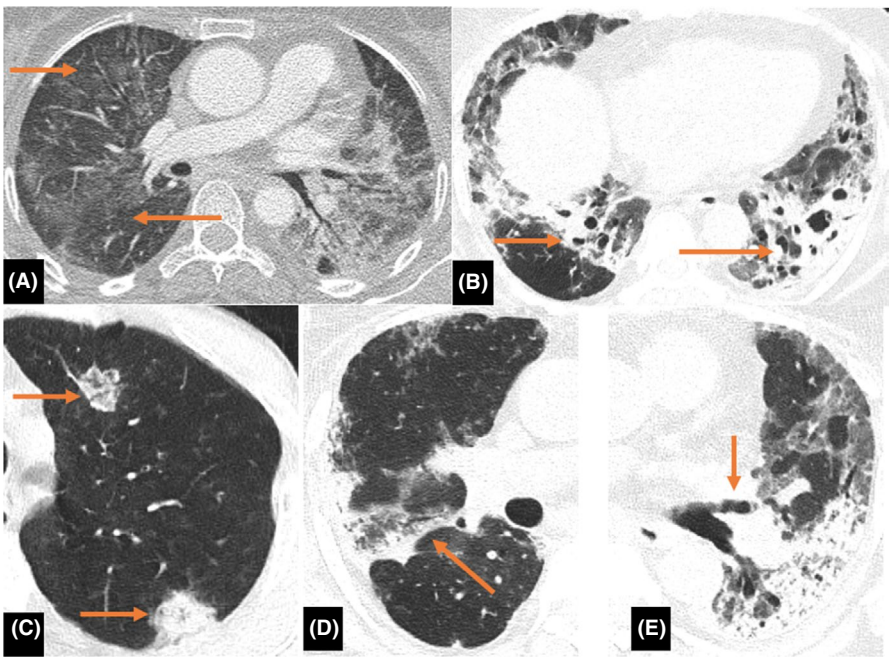

FIGURE 1 Ground glass opacity (GGO) predominant pulmonary changes due to background COVID-19-related changes in patients with COVID-19-associated SAIA. Axial CT images of different patients showing pure GGO (arrow) (A), GGO with peribronchial fibrosis (arrow) (D) and bronchiectasis (arrow) (B, E) and patchy focal consolidation and GGO with relative central clearing-atoll sign (arrow) (C). A-patient #5; B and C-patient #3; C- patient #3; D and E- patient #2

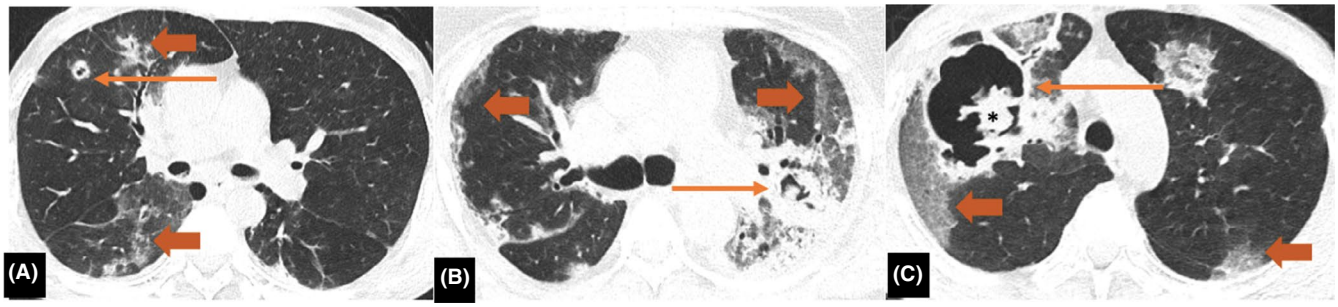

FIGURE 2 Cavitary changes in SAIA. Axial CT images of different patients show variable sized cavities (arrow) with associated ground glass opacities (block arrows). The large right upper lobe cavity (C) shows internal contents (*) likely to represent necrotising parenchymal tissue. A and C- patient #9; B- patient #2

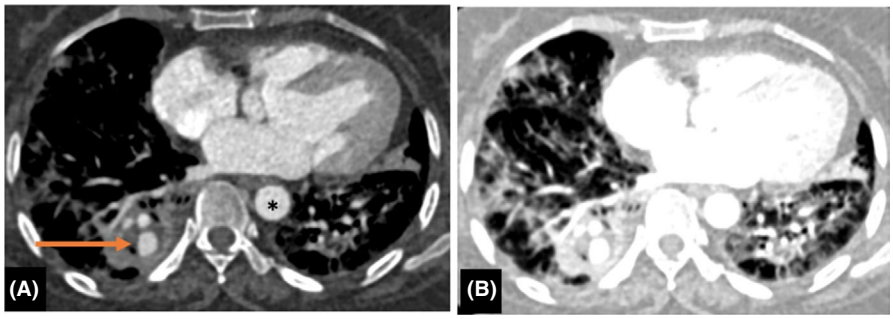

FIGURE 3 Pulmonary vascular complication in SAIA in patient #5. A pulmonary pseudoaneurysm is seen as contrast filled outpouchings (arrow) paralleling the contrast opacification of descending thoracic aorta (*) in the superior segment of the right lower lobe (A). The lung window (B) shows the ground glass opacities surrounding the pseudoaneurysm and in subpleural areas of both lungs. A and B—patient #5

present 10 cases of SAIA, occurring in the backdrop of COVID-19 and describe their clinico-radio-microbiological profile.

2 | PATIENT AND METHODS

2.1 | Study setting

We prospectively collected the data of all the patients, who were hospitalised between 1 May 2021 and 1 July 2021, who presented with recent history of COVID-19 (within 8 weeks of present hospitalisation), cavitary lung disease, positive IgG report (against *Aspergillus*) with or without respiratory secretions positive for *Aspergillus spp*. The clinico-demographic details, symptomatology, radiographic features, microbiological profile, treatment and outcome were entered in a pre-designed proforma. The diagnosis of severity of COVID-19 was based on WHO COVID-19 clinical guidelines 2021, wherein, all patients with peripheral oxygen saturation (SpO_2) <94% on room air at sea level, a respiratory rate >30 breaths/min, PaO2/FiO2 <300 mm Hg or lung infiltrates >50% were considered to have severe disease.[3] The diagnosis of SAIA was based on ERS and ESCMID 2016 guidelines for management of chronic pulmonary aspergillosis which also covered SAIA.[4] The patients were followed up till outcome (death or discharge) or four weeks from initial diagnosis of SAIA (whichever was earlier). A subsequent follow-up was done at end of 3 months from diagnosis of SAIA for all patients.

2.2 | Microbiological diagnosis

Fungal culture of respiratory samples was performed on Sabouraud dextrose agar and BHI (Brain Heart Infusion) agar, and positive cultures were identified using culture characteristics and microscopic morphology. Galactomannan (GM) in serum and blood was detected using Platelia™ Aspergillus (Bio-Rad Laboratories) with a cut-off index of ≥1.0 in serum and bronchoalveolar lavage (BAL). Fungal polymerase chain reaction (PCR) was performed using an in-house kit, following standard protocol. Serum antibody (IgG) against *Aspergillus* was performed using Platelia™ Aspergillus IgG (Bio-Rad Laboratories) via immune-enzymatic method or by Genesis™ Aspergillus IgG Kit via enzyme-linked immune-based assay (ELISA) with a cut-off >12 U/ml (for both).

2.3 | Ethics consideration

Ethics clearance for the study was taken from Institutional Ethical Committee (Ref. No. IECPG-392/23062021).

3 | RESULTS

The clinico-radio-microbiological characteristics of all the cases ($n = 10$; M:F = 6:4) are compiled in Tables 1 and 2. A total 1,737 patients with COVID-19 were admitted in our hospital between April and June 2021. Out of the 10 patients with SAIA, four patients were admitted in our institute from the beginning of their hospitalisation for COVID-19, while six patients were referred to us for continuing symptoms. The mean age of the patients was 50.7 ± 11.8 years. All patients had a history of recent COVID-19 illness and were admitted to our hospital with new-onset symptoms. The mean duration between diagnosis of SAIA and COVID-19 positivity was 29.2 ± 12 days. All of them had severe COVID-19 illness, with six patients (60%) being admitted in intensive care unit and four (40%) patients in general ward. All of them had received steroids for COVID-19 illness in variable doses and durations, as per local guidelines.[5] During the present hospitalisation, eight (80%) patients presented with cough as the predominant complaint, shortness of breath was present in five (50%) and haemoptysis was seen in four (40%) of them. Seven (70%) patients were known diabetic with a mean HbA1c of 8.5 ± 2.1% (HbA1c range: non-diabetic <5.6%, pre-diabetic 5.7%-6.4% and diabetic ≤6.5%), while all had steroid-induced hyperglycaemia during treatment course for COVID-19. Other comorbidities included hypertension in two patients, coronary artery disease in one patient and lymphoma in one patient. All patients (100%) were positive for serum IgG antibody against *Aspergillus*. Serum galactomannan was sent for 9 patients and was positive in five (55.55%). Fungal culture of respiratory samples was positive for *Aspergillus fumigatus* in two patients (28.5%) out of seven patients whose sample could be sent. One patient had mixed infection with mucormycosis, based on sputum KOH, showing both septate and aseptate hyphae. Polymerase chain reaction (PCR) for Aspergillus was performed on respiratory fluid (BAL fluid) in three patients of which all were positive. Other important differential for cavitary lesion like tuberculosis was ruled out in eight (80%) patients by sputum or BAL GeneXpert™.[6]

All patients underwent chest computerised tomography (CT), eight patients (80%) had a single cavitary lesion while two patients (20%) had multiple cavitary lesions. Post-COVID changes like ground glass opacities and septal thickening were present in all patients; while fibrotic bands were noted in four patients (40%). Representative CT findings are depicted in Figures 1 and 2. Other additional findings like pseudoaneurysm of pulmonary artery were seen in two patients as shown in Figure 3. All patients were treated with voriconazole. During the initial 28 days of the study, three patients had died (two patients died due to sepsis-associated progressive respiratory failure while one patient died due to gallstone-induced pancreatitis during hospital stay), six patients were discharged and one patient remained hospitalised. At ~90 days (from day of diagnosis of SAIA), one patient died (due to progressive respiratory failure associated with ventilator-associated pneumonia), while the remaining six patients showed steady improvement. Two patients were discharged and continued to use oxygen till the end of the period (with gradual reduction in oxygen requirement). The remaining four patients did not require oxygen after discharge, out of which one patient-reported exercise intolerance. Two patients had repeat CT done between 60 and 90 days (from day of diagnosis of SAIA) which showed significant reduction in cavity size with persisting radiological features of COVID-19 sequelae.

4 | DISCUSSION

We present a cohort of patients with COVID-19-associated SAIA having recent diagnosis of COVID-19. Majority of the patients had diabetes and all had received steroids for their COVID-19 condition. All of them presented with cavitating lung disease, IgG *Aspergillus* positivity and most had *Aspergillus spp* isolated from their respiratory samples. The initial reports describing chronic necrotising pulmonary (CNPA) aspergillosis, date back to more than 50 years.[7] The first reference of SAIA, a term which is used interchangeably with CNPA, appears to have been made in 1983 by Gefter et al.[8] SAIA refers to the slowly progressive form of invasive aspergillosis, usually seen in mildly immunocompromised patients.[9] The disease usually progresses over 1–3 months and presents with variable radiological features like cavitation, nodules or consolidation.[10] The immunocompromising conditions reported include diabetes mellitus, malnutrition, old age, alcoholism, COPD, connective tissue disorder, radiation therapy, HIV infection, non-tuberculous mycobacterial infection(NTM) and low-dose corticosteroid therapy.[7] Steroid therapy (dose as low as 5–20 mg every other day) and recent influenza infection[11] have been implicated as predisposing factors for this disease. Inhalation of *Aspergillus* spores is thought to lead to colonisation of respiratory tract, even in health. In the backdrop of diminished immunity, germination into hyphal elements and subsequent invasion of lung parenchyma can occur, leading to SAIA. In all patients in our series who suffered from COVID-19 recently, steroid administration was a common predisposing condition and diabetes was present in the vast majority. Respiratory viruses, incidentally, are also known to cause direct damage to airway mucosa,[12] impair ciliary clearance,[13] cause immunosuppression especially in the background of ARDS,[14] while COVID-19 specifically has been linked to decreased T-cell number and activity.[15] In the light of the above, it is plausible that the combination of hyperglycaemia[16] (due to steroids use with or without pre-existing diabetes) along with severe COVID-19 played a role in the genesis of SAIA in our cohort of patients.

COVID-19 infection has been implicated previously with pulmonary aspergillosis (CAPA).[17–20] Incidentally, other fungal infections like COVID-19-associated mucormycosis has also been reported in relation to this ongoing pandemic; however, the pathophysiological factors are yet to be determined.[21–23] This is the first case series that describes the more indolent form of aspergillosis—SAIA in the backdrop of COVID-19. SAIA had been described in a previous patient of COVID-19 with features of lung cavity with fungal balls and isolation of *Aspergillus flavus* from sputum.[24] The diagnosis of SAIA hinges on the demonstration of IgG antibody or *Aspergillus* antigen in the setting of a clinical picture of progression

of disease over 1–3 months typically in a mildly immunocompromised patient.[4] Biopsy, if done, may demonstrate lung parenchymal invasion by fungal hyphae. Treatment of this disease usually involves antifungal agents, for example voriconazole given typically for ~10 months, as in other forms of chronic pulmonary aspergillosis.[25–27] Surgical resection, indicated for necrotic lung with ongoing features of sepsis, is often not required or becomes risky because of patient's poor general health.

The limitations of our present study are the small number of cases, absence of histopathological corroboration and data about genetic defects which can predispose to chronic pulmonary aspergillosis. Future studies should focus on unravelling these aspects of SAIA, occurring in patients with recent COVID-19.

In conclusion, SAIA should be considered in the differential diagnosis of cavitating lung lesions in patients with recent history of COVID-19 in the background of steroid use with or without pre-existing diabetes. Early diagnosis and prompt treatment can help in appropriate management of such cases.

CONFLICT OF INTEREST

None.

AUTHOR CONTRIBUTION

Satish Swain: Conceptualization (lead); Formal analysis (equal); Investigation (equal); Methodology (equal); Writing-original draft (lead); Writing-review & editing (equal). Animesh Ray: Conceptualization (lead); Formal analysis (equal); Investigation (equal); Methodology (equal); Supervision (lead); Writing-original draft (lead); Writing-review & editing (lead). Radhika Sarda: Data curation (equal); Investigation (equal); Methodology (equal); Resources (equal). Surabhi Vyas: Data curation (equal); Methodology (equal); Resources (equal); Validation (equal); Writing-original draft (equal); Writing-review & editing (equal). Gagandeep Singh: Investigation (equal); Methodology (equal); Resources (equal); Writing-review & editing (equal). Pankaj Jorwal: Data curation (equal); Investigation (equal); Methodology (equal); Project administration (equal); Writing-original draft (equal). Parul Kodan: Investigation (equal); Methodology (equal); Project administration (equal); Writing-original draft (equal). Puneet Khanna: Project administration (equal); Resources (equal). Immaculata Xess: Investigation (equal); Resources (equal); Writing-review & editing (equal). Sanjeev Sinha: Supervision (equal); Writing-review & editing (equal). Naveet Wig: Supervision (lead); Validation (equal); Writing-review & editing (equal). Anjan Trikha: Project administration (equal); Resources (equal); Supervision (equal).

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ORCID

Satish Swain https://orcid.org/0000-0001-9466-3531
Animesh Ray https://orcid.org/0000-0002-9434-5338

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