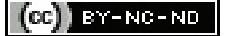


Radiological Findings of Thoracic Sarcoidosis in an Indian Cohort: A Retrospective Study

THARANI PUTTA¹, APARNA IRODI², RV LEENA³, BINITA RIYA CHACKO⁴, DEVASAHAYAM CHRISTOPHER⁵

ABSTRACT

Introduction: Sarcoidosis is commonly mistaken for tuberculosis in India. Imaging is of paramount importance in making a correct diagnosis, but, most of the published literature available on radiological findings of sarcoidosis is from the Western population.

Aim: To study the radiological findings of thoracic sarcoidosis in Indian patients.

Materials and Methods: This was a retrospective descriptive study done in a tertiary hospital in Southern India after obtaining clearance from Institutional Review board and Ethics Committee (IRB Min no 6997). Ninety-six patients diagnosed with sarcoidosis between January 2001 and August 2009 based on a combination of clinical, radiological and histopathological findings were included in the study. Their chest radiographs and High-Resolution Computerised Tomography (HRCT) thorax at presentation were reviewed and radiological findings were documented on a proforma. Statistical Package for the Social

Sciences (SPSS, IBM Corp., Armonk, NY) software version 21.0 was used for statistical analysis.

Results: The HRCT was abnormal in all the study patients with lymphadenopathy seen in 87 patients (90.6%) and lung parenchymal abnormality in 92 patients (95.8%). Mediastinal nodes were more commonly seen when compared with hilar lymphadenopathy. The typical lung parenchymal findings seen were juxta-fissural or subpleural nodules and peribronchovascular nodular interstitial thickening. Late irreversible findings were seen at least focally in 43 patients (45%). The classically described upper zone lung predilection was not seen in this study.

Conclusion: Paratracheal and subcarinal lymphadenopathy are more common than hilar lymphadenopathy in sarcoidosis. Despite overlapping radiological findings between pulmonary sarcoidosis and tuberculosis, the presence of hyperdense nodes, fissural nodularity, peribronchovascular nodular interstitial thickening with perihilar prominence of findings should favour diagnosis of sarcoidosis.

Keywords: High resolution computed tomography, Hyperdense nodes, Interstitial thickening, Perilymphatic nodules

INTRODUCTION

Sarcoidosis is an idiopathic disorder affecting multiple systems and is characterised by the formation of non caseating granulomas. Pulmonary involvement is described in 90% of patients and 20% of these patients may progress to pulmonary fibrosis [1] and permanent functional impairment. Sarcoidosis is known for its wide range of clinical and radiological presentation. In India, sarcoidosis is underdiagnosed, often mistaken for tuberculosis because of the close resemblance in their clinical and radiological presentation and also in the histopathological appearance [2]. Knowledge of various patterns of radiological presentation of sarcoidosis is important to aid in accurate diagnosis of this condition. HRCT thorax is superior to chest radiograph and conventional CT for diagnosis and assessing disease extent and severity [3]. Magnetic Resonance Imaging (MRI) has a complementary role when there is suspicion of myocarditis, but is inferior to HRCT for detecting lung parenchymal involvement owing to superior spatial resolution of CT compared to MRI. This retrospective descriptive study aims to study the spectrum of imaging findings of thoracic sarcoidosis in Indian patients and to highlight any differences when compared to the literature from rest of the world, with emphasis on HRCT findings.

MATERIALS AND METHODS

This was a retrospective descriptive study done in a tertiary care hospital in Southern India after obtaining clearance from Institutional Review board and Ethics Committee (IRB Min no 6997).

Inclusion and exclusion criteria: Study included all patients diagnosed with thoracic sarcoidosis between January 2001 and August 2009. Confirmation of diagnosis was based on clinical, radiological, histopathological findings and response to appropriate treatment. When in doubt, final diagnosis was agreed upon in multidisciplinary

meetings comprising pulmonologists, chest specialist radiologists and pathologists. Patients who did not have either histopathology (or) HRCT thorax, with sputum positive pulmonary tuberculosis (or) histopathology highly suggestive of tuberculosis were excluded from the study. Chest radiograph and HRCT findings were reviewed by the radiologist.

Study Procedure

The HRCT thorax was done on one of the two scanners: 16 slice Siemens Somatom Emotion or 6 slice Philips Brilliance, with 1-1.5 mm slice thickness, 1.5-3 mm collimation, 768×768 matrix size and 30 cm Field of View (FOV). High spatial frequency reconstruction algorithm was used. Images were acquired in full inspiration and with the patient in supine position; additional prone CT and expiratory CT with spaced acquisition were done in a few patients in accordance with the indication for CT scan. Lung and mediastinal windows were used for reading the CT scan.

The International Association for the Study of Lung Cancer (IASLC) lymph node stations were used for categorising lymph nodes with short axis diameter cut-off of 10 mm. Note was made of the presence or absence of any nodal calcification and type of calcification, presence or absence of any hyperdensity within the nodes (density compared to the mediastinal vascular structures). Lung parenchymal findings that were evaluated included: presence of micronodules (1-4 mm), macronodules (>5 mm) and their distribution in the form of nodular peribronchial interstitial thickening, nodular interlobular septal thickening, juxta-fissural and subpleural nodularity, centrilobular nodules, large or confluent nodules (>1 cm), galaxy sign [4], fairy ring sign [5], consolidation, cavitation, fibrosis, traction bronchiectasis and honeycombing, bronchiectasis with adjacent areas of consolidation. Note made of the predominant

distribution of findings in upper, mid and lower lung zones and central vs peripheral lung parenchyma. Free text section was also added and all the radiological findings and basic demographic data were entered in a structured proforma, for further analysis.

STATISTICAL ANALYSIS

Frequency of findings was given in percentages (rounded to the nearest integer or first decimal point). Statistical Package for Social Packages (SPSS), IBM Corp., Armonk, NY) software version 21 was used for statistical analysis.

RESULTS

A total of 96 patients who were diagnosed to have thoracic sarcoidosis were included in the study. Age of the study population ranged from 26-77 years (mean age=45.4 years; SD 11 years) and 70 patients (73%) were between 31-60 years of age. Rest belonged to ≤30 years or >60 years age group. A total of 53 (55%) were women and 43 (45%) were men and comprised of people from varied geographic locations within India.

Chest radiograph: Chest radiograph at presentation was abnormal in 85 (88.5%) patients while HRCT was abnormal in 100%. Intrathoracic lymphadenopathy was seen in 51 (53%) of the chest radiographs and the frequency of various lymph nodal sites involvement is given in [Table/Fig-1]. Lung parenchymal involvement was seen on chest radiograph in 66 (68.7%) patients while the remaining 30 (31.3%) patients had normal appearing lungs on the chest radiograph. The common patterns seen on chest radiograph were reticulonodular opacities, consolidation, scarring and collapse. Lung parenchymal findings on chest radiograph were not specific for sarcoidosis and chest radiograph has a limited role in the initial diagnosis of patients with thoracic sarcoidosis.

Location	Number (Frequency, %)
Bilateral hilar	17 (33.3)
Unilateral hilar	6 (11.7)
Paratracheal	17 (33.3)
Aorto-pulmonary window	9 (17.6)
Subcarinal	3 (5.8)
Para-oesophageal	3 (5.8)
"1-2-3 sign"	12 (23.5)

[Table/Fig-1]: Frequency of various sites of lymph node enlargement as seen on chest radiograph. Multiple sites were involved in many patients. Total N=51. 51 was only the no. of cases with lymph nodes on chest X-ray, as mentioned; 85 was the no. of cases with abnormal chest X-ray (includes both lymph nodes and parenchymal findings)

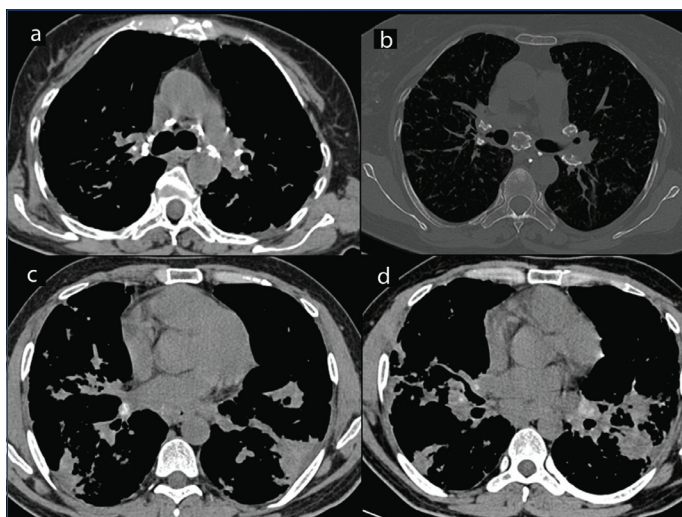
High Resolution CT thorax

a) Nodal involvement: Thoracic lymphadenopathy was seen in 87 of the 96 study patients (90.6%) on HRCT. HRCT helped identify lymphadenopathy in 37.6% of the patients whose chest radiographs did not show enlarged lymph nodes. Frequency of lymph node enlargement at each of the locations is provided in [Table/Fig-2]. An 18 out of 87 patients (20.6%) showed lymph node calcification [Table/Fig-3a-c], most commonly the nodular type (n=13; 14.9%) followed by the classically described egg-shell type (n=3; 3.4%) and amorphous type (n=2; 2.3%) of calcification. Some of the lymph nodes appeared hyperdense as compared to the adjacent vessel [Table/Fig-3d], on non contrast CT and this finding was recorded in 10 out of 96 (10.4%) of the patients.

b) Lung parenchymal involvement: Lung parenchymal abnormality was noted in 92 out of 96 (95.8%) patients [Table/Fig-4]. Remaining four patients had thoracic lymphadenopathy without lung parenchymal abnormality on HRCT. The common and less common patterns of lung parenchymal involvement are listed in [Table/Fig-5]. The three commonest findings (juxta-fissural/subpleural nodularity, peribronchovascular interstitial nodularity, nodular interlobular septal thickening) will be hitherto referred to as "typical" findings or patterns,

Location	Number (Frequency, %)
Hilar	63 (72.4)
Bilateral hilar	57 (65.5)
Unilateral hilar (right)	6 (6.9)
Paratracheal	74 (85)
Bilateral paratracheal	45 (51.7)
Right paratracheal only	28 (32.2)
Left paratracheal only	1 (1.1)
Aorto-pulmonary window	49 (56.3)
Subcarinal	66 (75.8)
Para-oesophageal	31 (35.6)

[Table/Fig-2]: Frequency of different sites of lymph node enlargement as seen on HRCT thorax. Multiple sites were involved in many patients. Total N=87

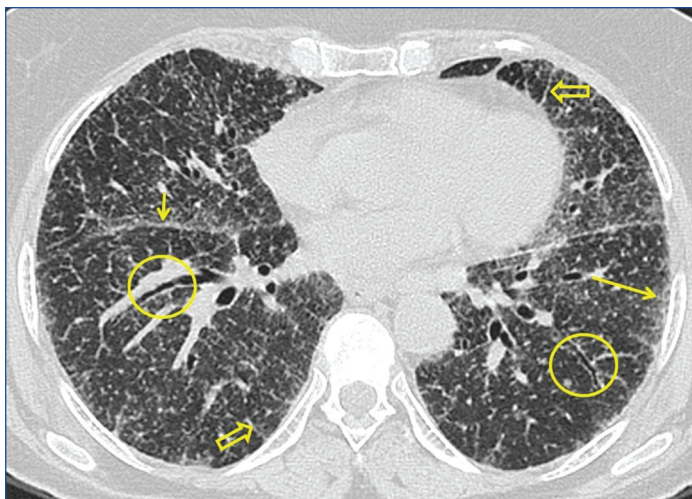


[Table/Fig-3]: Showing various types of lymph nodal calcification on HRCT thorax; a) dense nodular calcification; b) egg shell calcification; c) amorphous calcification; d) shows hyperdense bilateral hilar lymph nodes.

for the rest of the article. Atleast one of the typical patterns was seen in 81 (84.3%) of 96 study patients. A combination of two or more findings were seen in 64 patients (66.6%) and all three patterns were seen in 39 patients (40.6%). Mosaic attenuation was not always associated with appreciable airway narrowing. Expiratory scans were not available in most of these patients to confirm the cause of mosaic attenuation. In one patient, the radiological findings resembled Non Specific Interstitial Pneumonia (NSIP) pattern [Table/Fig-6]. "Galaxy sign" defined as coalescent lung parenchymal nodules surrounded by many tiny satellite nodules giving the appearance of a galaxy was

Finding	Number (Frequency, %)
Juxta-fissural/subpleural nodularity*	74 (77)
Peribronchovascular interstitial nodularity*	58 (60.4)
Nodular interlobular septal thickening*	52 (54.1)
Centrilobular nodules	16 (16.6)
Discrete nodule of >1cm size	6 (6.2)
Consolidation	33 (34.3)
Ground glass opacities	30 (31.2)
Airway narrowing	19 (19.8)
Mosaic attenuation	21 (21.8)
Sarcoid galaxy	9 (9.3)
Cavitating nodules	2 (2.1)
Architectural distortion, bronchiectasis, honeycombing, fibrosis	43 (44.8)
End stage pulmonary fibrosis	2 (2.1)

[Table/Fig-4]: Frequency of various lung parenchymal findings as seen on HRCT thorax. More than one finding was seen in many patients. Total N=96; *Indicates typical lung parenchymal findings of sarcoidosis

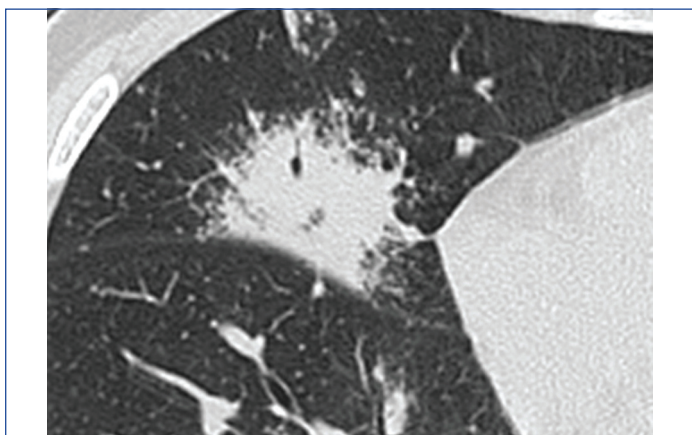


[Table/Fig-5]: Axial HRCT image in lung window showing nodular fissural thickening (short arrow), subpleural nodularity (long arrow), beading along the bronchial wall (circle) and interlobular septal thickening (open arrows).



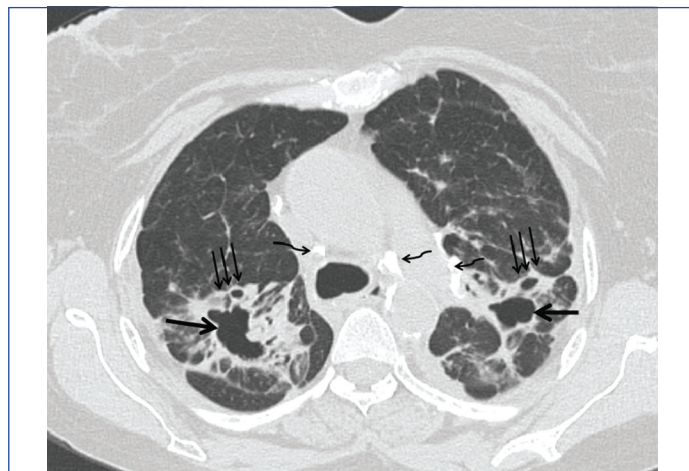
[Table/Fig-6]: Axial HRCT image in lung window of a patient with sarcoidosis showing irregular reticular lines, ground glass density and architectural distortion in the form of traction bronchioectasis with basal and subpleural predominance, suggestive of NSIP pattern of lung involvement.

seen in 9 (9.3%) patients [Table/Fig-7]. "Fairy ring sign" defined as alveolar sarcoid with a central necrotic appearance on mediastinal window while the lung window shows central normal aerated lung tissue was not seen in any of the study patients. Architectural distortion, bronchiectasis, honeycombing or fibrosis were seen at least focally in 43 patients (44.8%) while end stage pulmonary fibrosis was seen only in 2 patients (2.1%) [Table/Fig-8]. There was no zonal predilection of lung involvement in 40 (41.6%) patients and among the rest, the frequency of involvement of each of the three lung zones (upper, mid and lower) was similar. Central/perihilar lung was more often involved (n= 22; 22.9%) than the peripheral lung parenchyma



[Table/Fig-7]: Axial HRCT image in lung window showing numerous tiny nodules at the periphery of a confluent lung parenchymal lesion, termed 'galaxy sign'.

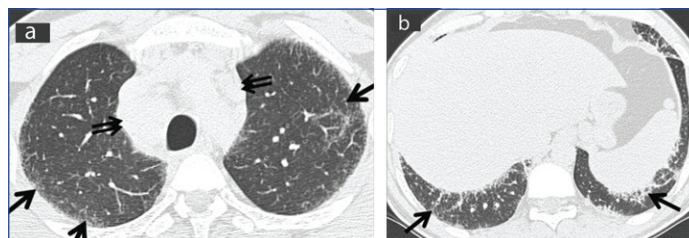
(n=13; 13.5%) [Tables/Fig-9,10]. There was no pleural effusion in any patient at presentation. Concomitant upper abdominal lymph node enlargement was detected in 11 (11.4%) patients. Splenomegaly was seen in 16 patients (16.6%) while hepatomegaly was seen in only 4 patients (4.1%). In three of the study cases, CT showed very typical findings of sarcoidosis and few coexisting findings favouring tuberculosis; dual diagnosis of sarcoidosis coexisting with tuberculosis was made in these patients.



[Table/Fig-8]: Axial HRCT images in lung window through upper lobes in a patient with stage 4 sarcoidosis, showing conglomerate areas of scarring in both upper lobes (thin arrows), with cavitation (thick arrows). Calcified mediastinal nodes are also seen (thin curved arrows).



[Table/Fig-9]: Axial HRCT image in lung window through upper lobes, showing perilymphatic nodules along central peribronchial interstitium (straight arrows) and perivascular interstitium (curved arrows).



[Table/Fig-10]: Axial HRCT images in lung window through upper lobes (a) and lung bases (b) in the same patient, showing peripheral subpleural nodular intra and interlobular septal thickening (black arrows in a and b), and significant lower lobe involvement (black arrows in b). Significant mediastinal lymphadenopathy is also present (double arrows in a).

DISCUSSION

Chest radiograph: Only 12% of the patients had normal chest radiograph at initial presentation, which is comparable to what has been documented in the literature [5,6]. Bilateral hilar adenopathy was thought to be the most common radiographic finding in earlier studies [7,8], while this study showed bilateral hilar nodes and paratracheal nodes with comparable frequency. Unilateral hilar adenopathy was also more common (12%) than what has been described [9,10]. The classically described radiological pattern of bilateral hilar nodes with right paratracheal adenopathy in sarcoidosis, also known as “1-2-3 sign” or “pawn broker’s sign” [4] was seen in only 23.5% of the study patients and absence of this sign therefore does not make the diagnosis less likely.

High resolution CT thorax: The HRCT showed paratracheal lymphadenopathy in 85% of the patients while hilar lymphadenopathy was seen only in 72.4% of the patients. This contradicts the earlier belief that paratracheal node enlargement is rarely seen without concomitant hilar lymphadenopathy [11]. Bilateral paratracheal nodes were more common than isolated right or left paratracheal nodes and similarly, bilateral hilar nodes were also much more common than isolated right hilar nodes. Aorto-pulmonary, subcarinal and para-esophageal nodes were seen in a significant number of the study patients. Para-esophageal nodes (35.6%) were much more frequently seen in this study when compared to other studies [11-14]. About one-fifth of patients showed lymph nodal calcification which was frequently nodular or solid type [15]. In an additional 10% of cases, there were “hyperdense nodes” which appear denser than the adjacent vascular structures on HRCT without overt calcification. To the best of knowledge, the present study finding has not been described earlier in literature. The authors believe that this sign could be useful in aiding prospective diagnosis of sarcoidosis in patients with undiagnosed thoracic lymphadenopathy without any typical lung parenchymal findings.

The CT showed lung parenchymal abnormality more commonly than lymphadenopathy (96% vs 91%) in the study population contrary to what has been reported in literature [1,12,13]. This could be due to referral bias (study conducted at a tertiary care referral hospital). Lung parenchymal involvement in sarcoidosis is characterised by involvement of the pulmonary interstitial lymphatics in the form of nodular interlobular septal thickening, nodular peri-bronchovascular interstitial thickening and subpleural (including juxta-fissural) nodules. These nodules are typically small measuring approximately 1-10 mm, distributed mainly along the interstitial lymphatics [1,16-19]. At least one or more of these typical lung findings were seen in 84% of the cases, and the remaining 16% had mediastinal and hilar lymphadenopathy. Histopathological examination of the lung biopsy slides showed granulomas (predominantly non caseating granulomas) in all the study patients including those who did not have any lung parenchymal abnormality on HRCT, suggesting that even a good quality high resolution CT may be potentially underestimating the presence and severity of interstitial granulomas. The single most common lung parenchymal finding seen in this study was fissural or subpleural nodularity (77%) followed by nodular peri-bronchovascular interstitial thickening (60.4%) and interlobular septal thickening (54.1%). There was no zonal predilection for lung parenchymal involvement. Centrilobular interstitial involvement was much less common, seen in less than one-fifth of the cases. In all the cases with centrilobular interstitial involvement, there was also a combination of at least two or more of the typical lung parenchymal findings making the diagnosis fairly straightforward. Small lung nodules may coalesce or become confluent giving rise to larger nodules and areas of consolidation which was seen in one-third of the study cases. One-fifth of the patients had bronchocentric or peri-bronchial consolidation resulting in airway narrowing. “sarcoid galaxies” [4] may be seen in some of

these patients (9.3% in the present study). The larger nodules or consolidation may occasionally show evidence of cavitation (2.1% of our cases) which is comparable to that of other studies [1,20]. This finding is suggestive of granulomatous angiitis [1,21]. In this small subset of cases, tuberculosis was considered as the most likely diagnosis at initial presentation. In these patients, the final diagnosis of necrotising sarcoidosis could be made based on lack of response to prior Anti-Tuberculous Therapy (ATT) and clinical improvement following a few months of corticosteroid therapy.

There is no zonal predilection of lung parenchymal findings in this study contrary to the common belief that sarcoidosis preferentially involves upper-mid zones or upper lobes of lungs [19,21]. Vast majority of the patients with lung parenchymal involvement show fairly uniform involvement of central and peripheral lung parenchyma (60%). This finding contradicts the “centrifugal pattern” of disease that is classically described in literature [16]. Therefore, it is recommended that when the typical CT findings of sarcoidosis are present, lack of centrifugal disease pattern and lack of upper lobar predominance must not refute the diagnosis of sarcoidosis.

Patchy areas of ground glass opacity may also be seen in the involved segments. This could be because of tiny nodules which cannot be resolved on CT [1]. In one patient, the HRCT findings resembled NSIP pattern and an initial diagnosis of sarcoidosis could not be confidently made in this patient.

In the advanced stage, lung parenchyma shows varying degrees of architectural distortion, traction bronchiectasis, honeycombing and collapse. Two of the study cases showed irreversible end stage pulmonary fibrosis at presentation. In some cases when there is no prior imaging for comparison or histopathological correlation is not possible. In such cases, establishing aetiology for fibrosis and specific imaging diagnosis becomes extremely challenging, once again re-emphasising the vital role of a multidisciplinary team in diagnosis. Three of the study patients had co-existing pulmonary tuberculosis and sarcoidosis. These patients initially received ATT with which the findings related to tuberculosis improved and there were persistent sarcoidosis related findings on HRCT. Subsequently, they received steroids for sarcoidosis treatment and showed good response.

One of the main strong points of this study is the fairly large sample size and availability of long term follow-up (useful in assessing response to treatment thereby confirming the diagnosis in some cases).

Limitation(s)

One of the limitations of this study is referral bias resulting in a larger subset of study population showing more advanced disease, that further contributed to the delay in diagnosis.

CONCLUSION(S)

The HRCT is an invaluable tool aiding in diagnosis of sarcoidosis and assessing of extent of disease and one cannot emphasise enough on the role of multidisciplinary team in establishing the diagnosis. Despite the overlapping radiological findings between pulmonary sarcoidosis and tuberculosis, the presence of hyperdense nodes, fissural nodularity, peribronchovascular nodular interstitial thickening with perihilar prominence of findings should favour the diagnosis of sarcoidosis. One should also remember that the presence of perilymphatic nodules in peripheral distribution, asymmetric or unilateral lymph nodes, predominant mediastinal lymphadenopathy, significant involvement of lower lobes or absence of upper zone predominance should not preclude the clinician from making the diagnosis of sarcoidosis.

Acknowledgement

We declare that all persons who have made substantial contribution to the work reported in the manuscript have been included as authors.

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PLAGIARISM CHECKING METHODS: [Jain H et al.]

- Plagiarism X-checker: Dec 22, 2020
- Manual Googling: May 06, 2021
- iThenticate Software: May 28, 2021 (5%)

ETYMOLOGY: Author Origin

AUTHOR DECLARATION:

- Financial or Other Competing Interests: None
- Was Ethics Committee Approval obtained for this study? Yes
- Was informed consent obtained from the subjects involved in the study? Yes
- For any images presented appropriate consent has been obtained from the subjects. NA

Date of Submission: **Dec 21, 2020**

Date of Peer Review: **Mar 17, 2021**

Date of Acceptance: **May 07, 2021**

Date of Publishing: **Oct 01, 2021**