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Impulse oscillometry as a measure of airway dysfunction in Sarcoidosis

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Abstract. *Background*: Sarcoidosis is a systemic inflammatory granulomatous disease which commonly affects intrathoracic lymph nodes, lung parenchyma and airways. *Objectives*: To measure respiratory impedance using Impulse Oscillometry (IOS) in patients with pulmonary sarcoidosis and compare the parameters with healthy controls. *Methods*: Patients diagnosed with sarcoidosis (n=28); and age and gender matched healthy controls (n=17) were recruited. Lung volumes and capacities were measured by spirometry and respiratory system impedance was assessed using Impulse Oscillometry System (IOS). Measurements were performed before and 15 minutes after inhalation of a short acting bronchodilator. The IOS and spirometric parameters were compared between two groups and correlated. ROC curve analysis was also performed to identify the IOS parameters which can discriminate between sarcoidosis and healthy controls. *Results*: Resistance at 5 and 20 Hz (R5 and R20), small airway resistance (R5-R20), resonant frequency (F_{Res}) and area of reactance (AX) were significantly higher in Sarcoidosis subjects compared with controls. Reactance at 5 and 20 Hz (X5 and X20) were significantly lower in sarcoidosis. FEV_1 (% predicted) and FVC (% predicted) were significantly lower in patients with sarcoidosis while FEV_1/FVC ratio and peak expiratory flow rate (PEF) values were comparable. Post bronchodilator inhalation, there was improvement in airway resistance and reactance, but no significant changes observed in spirometric parameters. R5, X5 and R5-R20 are promising parameters to discriminate sarcoidosis from healthy controls. *Conclusion*: Increased airway resistance is a better indicator of airway involvement than airflow limitation by spirometry in pulmonary sarcoidosis.

Key words: Sarcoidosis, Spirometry, Airway resistance, Airway reactance, Respiratory impedance

Introduction

Sarcoidosis is a systemic inflammatory granulomatous disease of unknown etiology characterised by a varied spectrum of clinical presentations and histological presence of non-caseating granulomas, a pathologic hallmark of the disease. Multisystem involvement is the characteristic feature of sarcoidosis and can affect any organ like lungs, lymph nodes, eyes, skin, liver, heart, and central nervous system (1–4). The diagnosis of sarcoidosis is commonly based on radiological and clinical manifestations. The characteristic radiological findings associated with sarcoidosis have been well described and bilateral hilar lymphadenopathy is the most common finding, followed by parenchymal abnormalities (5,6).

Clinical staging based on radiological screening of patients with Pulmonary Sarcoidosis is as follows; stage 0- normal chest radiograph and no involvement of lungs (05-10% of patients); stage I- bilateral

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hilar lymphadenopathy (45-60% of patients); stage II- mixed pattern i.e. both lymphadenopathy and lung parenchymal disease (25-30% of patient); stage III - lung parenchymal infiltrates (15% of patients) and finally, end stage i.e. stage IV is pulmonary fibrosis (7,8).

Sarcoidosis affects lung parenchyma and airways in nearly two-third patients. Danila et. al. have reported significant difference in all spirometric parameters among sarcoidosis patients with different radiographic stages (9). They also observed that forced vital capacity (FVC), vital capacity (VC) and total lung capacity (TLC) tend to decrease with increase in broncho-alveolar lavage (BAL) fluid neutrophil and eosinophil count. Ors et. al. reported significant correlation between spirometric parameters and HRCT total scores and HRCT pattern scores (10). Suzuki et.al. observed significantly increased R5 and R5-R20 values (measured on Impulse Oscillometry) in patients with pulmonary sarcoidosis as compared to controls and negative correlation between R5-R20 and FEV_1 (11). Tanizawa et. al. reported natural course of pulmonary sarcoidosis without systemic treatment for 41.5 (12-78) months (12). On comparing baseline spirometric and IOS parameters, they concluded that decreased X5 and increased AX at the time of diagnosis were predictive of progressive pulmonary disease than airflow limitation on spirometry. Kiani et.al. have reported that peak VO_2 (% predicted) correlates positively with FVC (% predicted) while oxygen pulse correlates positively with body mass index, FVC(% predicted) and FEV_1(% predicted) which suggests that ventilatory limitation is one of the important causes for decreased exercise capacity in patients with sarcoidosis (13).

Clinical presentation of sarcoidosis in Indian patients differs significantly as compared to western population with pulmonary involvement in majority (90%) of patients (14). There are very few studies available investigating the airway mechanics and its relationship with changes in lung volumes and capacities in sarcoidosis.

The aim of this study was to evaluate lung volumes, capacities and airway impedance in patients with sarcoidosis. Impulse oscillometry system (IOS) was used to measure respiratory impedance which consists of resistance and reactance. It is a non-invasive method which requires minimal efforts from the subject and has much greater sensitivity to detect small airway disease in comparison to spirometry. The IOS generates small pressure oscillations of different frequencies that when travel through air passages cause change in the pressure which subsequently drives change in airflow. These changes help in determining the pulmonary airway resistance and reactance which are most important components of respiratory impedance (15).

Methods

Ethics statement

The study protocol was approved by the Institute Ethics Committee, All India Institute of Medical Sciences, New Delhi, India (IEC/365/6/2016) for research in human subjects. Written informed consent was obtained from all the subjects before enrolment in the study.

Selection of subjects

We recruited 28 patients diagnosed with Sarcoidosis from the Pulmonary, Outpatient clinic at AIIMS, New Delhi and 17 healthy controls from various departments. Diagnosis of sarcoidosis (American Thoracic Society Criteria) was made on the basis of consistent clinico radiological features (16) along with histopathological presence of non-caseating epithelioid granulomas. Patients having other diseases like COPD, lung cancer, lymphoma, pulmonary tuberculosis, asthma, were excluded from the study. After enrolment in the study detailed history of symptoms was taken and physical examination was performed. Weight (kg) and height (cm) of all subjects were recorded.

Measurement of respiratory impedance

Respiratory system impedance was measured using impulse oscillometry system (Eric Jaeger, Hoechberg, Germany). It comprises of two components: respiratory resistance and respiratory reactance (amount of recoil generated against that pressure wave) at different frequencies, and is calculated from pressure and flow signals where pressure is in phase with flow (16,17). The IOS measurements were done (18) and bronchodilator reversibility was tested by

repeating the manoeuvre 15 minutes after inhalation of 200µg salbutamol.

During IOS measurements subjects were asked to sit with neck in neutral position. After applying nose clip, cheeks were supported firmly and measurement was performed for 60 s. Patients were asked to breathe normally while the loudspeaker near the mouth piece delivered sound waves of different frequencies over the range of 5 to 30 Hz which superimposed on spontaneous tidal breathing. Resistance and reactance measured at lower frequency oscillations such as 5Hz are designated as R5 and X5 respectively. Similarly, resistance and reactance at higher frequency of 20 Hz are designated as R20 and X20 respectively. Sound waves of low frequency (5 Hz) are transmitted deep into lungs up to alveoli so R5 gives total airway resistance. Sound waves of higher frequency (20 Hz) travel only proximally in larger airways so R20 provides central airway resistance. The difference between R5 and R20 (R5-R20) is considered to be an index of the small airway resistance. Reactance has two components, inertance and capacitance. Inertance is the inertia of air column and it is positive; capacitance reflects elasticity of lung and it is negative in sign. The resonant frequency (Fres) is the intermediate frequency at which the total reactance is 0, and reactance area (AX) is the integrated low frequency respiratory reactance (area under the curve) between 5 Hz and Fres. It reflects a composite index for reactance. Coherence is the correlation between airflow and pressure wave and if there is a mismatch between the airflow into the lungs and the amplitude of the pressure wave, it results into low coherence (ranging 0-1). Acceptable coherence values should be at least 0.8 or higher at 5 Hz and 0.9 or more at 20Hz, which demonstrate the reliability and quality of given IOS test performance (16,17,19).

Spirometry

Forced vital capacity was measured using a spirometer (Medisoft, Spiro Air) according to the American Thoracic Society and European Respiratory Society guidelines (20). The subject was asked to inhale maximally from tidal respiration to total lung capacity and then exhale as rapidly and as maximally as possible until no further volume is exhaled. Like impulse oscillometry, spirometry was also performed before and 15 minutes after inhaling short-acting bronchodilator. Forced expiratory volume in 1st second (FEV_1) and FEV_1/FVC are the most widely used parameters to measure the mechanical properties of lungs. In obstructive disorders FEV_1 and FEV_1/FVC ratio are reduced and in restrictive lung disorders FEV_1 and FVC are reduced while FEV_1/FVC ratio is normal or increased.

Statistics:

All the parameters are expressed as the mean ± standard deviation or median (IQR) depending upon their distribution. Intra group and intergroup comparisons of the spirometry and IOS parameters were performed using unpaired t test for parametric and Mann–Whitney *U*-test for non-parametric variables. Correlation between various parameters was tested by Pearson or Spearman correlation based upon distribution of variables. To identify the specific IOS parameters which have the potential for differentiating between sarcoid patients and healthy controls, Receiver Operating Characteristic (ROC) curve analysis was performed. A value of $p < 0.05$ was considered as significant difference. All statistical analysis was performed using the software GraphPad Prism (version 7).

Results

The demographic characteristics of 28 patients with sarcoidosis and 17 healthy subjects are given in the Table 1. Seven patients had stage I, 18 patients had stage II, 2 patients had stage III and 1 patient had stage IV sarcoidosis. Table 1 also shows spirometric parameters in sarcoidosis patients and controls. FEV_1(% predicted) (64.79 ± 21.08 Vs 100.7 ± 12.75; p= 0.0001) and FVC (% predicted) (70.89± 20.61 Vs 102.4 ± 9.63; p=0.0001) were significantly lower in patients than controls. FEV_1/FVC ratio and PEF values were comparable between patients and healthy controls.

The IOS indices for patients with sarcoidosis and controls are given in the Table 2. The resistance at 5 and 20 Hz i.e. R5 (0.55±0.15 Vs 0.36±0.06 [(kPa/(L/s)]; p=0.0001) and R20 (0.37(0.32-0.50) Vs 0.28(0.25-0.33) [(kPa/(L/s)]; p=0.0002) were significantly higher in sarcoidosis patients than control group. While reactance at 5 and 20 Hz i.e. X5

Table 1. Demographic data and comparison of Spirometric parameters between Sarcoidosis patients and controls

Parameters	Sarcoidosis (n=28)	Control (n=17)	p value
Age (years)	52.39 ± 10.58	51.24 ± 10.27	0.72
Smoking history (Current/Ex-smoker)	2/1	Nil	
FEV_1/FVC	77.34 (72.56-82.75)	79.97 (78.59-83.90)	0.11
FEV_1 (% predicted)	64.79 ± 21.08	100.7 ± 12.75	0.0001
FVC (% predicted)	70.89± 20.61	102.4 ± 9.638	0.0001
PEF (% predicted)	81.71 ± 19.83	92.12 ± 22.59	0.12

FEV_1: Forced Expiratory Volume in 1 second, FVC: Forced Vital Capacity, PEF: Peak Expiratory Flow. Values given are either Mean±SD or Median (IQR). p value <0.05 is considered as significant

Table 2. Comparison of Impulse Oscillometry parameters between Sarcoidosis patients and controls

Parameters	Sarcoidosis (n=28)	Control (n=17)	p value
R5 [(kPa/(L/s)]	0.55±0.15	0.36±0.066	0.0001
X5 [(kPa/(L/s)]	-0.19 (-0.26- -0.17)	-0.13 (-0.16- -0.10)	0.0003
R20 [(kPa/(L/s)]	0.37 (0.32, 0.50)	0.28 (0.25, 0.33)	0.0002
X20 [(kPa/(L/s)]	-0.014±0.06	0.025±0.034	0.0091
AX (kPa/L)	1.31 (0.86-2.37)	0.52(0.36-0.93)	0.0007
R5-R20 [(kPa/(L/s)]	0.13(0.09-0.19)	0.06(0.04-0.09)	0.0002
Fres (Hz)	20.71±5.32	17.02±3.74	0.0095

R5: Respiratory system resistance at 5 Hz, R20: Respiratory system resistance at 20 Hz, X5: Respiratory system reactance at 5 Hz, X20: Respiratory system reactance at 20 Hz, AX: Area of reactance, F_{res}: Resonant frequency. Values given are either Mean±SD or Median (IQR). p value <0.05 is considered as significant

[(-0.19(-0.26- -0.17) Vs -0.13(-0.16- 0.10) [(kPa/(L/s)]; p=0.0003] and X20 (-0.01±0.06 Vs 0.02±0.03 [(kPa/(L/s)]; p=0.0091) were significantly lower or more negative in sarcoidosis patients than control group. The parameters which are specific to small airways resistance i.e. R5-R20 (0.13(0.09-0.19) Vs 0.06(0.04-0.09) [(kPa/(L/s)]; p= 0.0002), Fres (20.71±5.32 Vs 17.02±3.74 Hz; p=0.0095) and AX 1.31(0.86-2.37) Vs 0.52(0.36-0.93) kP/L; p=0.0007) were also significantly increased in sarcoidosis patients as compared to healthy controls.

For further analysis, the patients were divided in to two groups based on post bronchodilator FEV_1/FVC ratio. Group A consists of patients having FEV_1/FVC ratio > 70% (n= 23) and group B consists of patients having FEV_1/FVC ratio < 70% (n= 5). IOS parameters were compared between patients from group A (FEV_1/FVC > 70% (n= 23)) and healthy control group (n=17). It was observed that IOS parameters like resistance R5 (0.52 ±0.13 Vs 0.36±0.06 [(kPa/(L/s)]; p=0.0001), R20 (0.32(0.32-0.43) Vs 0.28(0.25-0.33) [(kPa/(L/s)]; p= 0.001), R5-R20 (0.13±0.08 Vs 0.06±0.03[(kPa/(L/s)]; p= 0.0008), reactance X5 (-0.19(-0.25- -0.17) Vs -0.13(-0.16- -0.10) [(kPa/(L/s)]; p=0.0004), and AX (1.45±0.99 Vs 0.63±0.34 kPa/L]; p=0.003) were significantly higher in the group A (patient) as compared to the control group as given in table 3. Post bronchodilator inhalation, a significant improvement was observed in all IOS parameters but not in spirometric parameters (table 4).

The correlation analysis between IOS and spirometric parameters in sarcoidosis patients (n=28) showed that R5 correlates negatively with FEV_1 (r= -0.53, p=0.004), FEV_1/FVC (r= -0.37, p=0.04) and PEF (r= -0.49, p=0.008). While R5-R20 and AX show significant negative correlation with FEV_1, FVC and PEF (table 5).

To identify the IOS parameters which can differentiate between sarcoidosis and healthy controls, receiver operating characteristic (ROC) curve analysis was done. It was observed that almost all the IOS parameters i.e. R5, X5, R20, R5-R20 and AX have area under the curve (AUC) >0.8. R5, X5 and

Table 3. Comparison of Impulse Oscillometry and Spirometric parameters between Sarcoidosis patients having FEV1/FVC > 0.7 and controls

Parameters	Sarcoidosis (n=23) $FEV_1/FVC > 70\%$	Controls (n=17)	p value
R5 [(kPa/(L/s)]	0.52 ±0.13	0.36±0.06	0.0001
R20 [(kPa/(L/s)]	0.32(0.32-0.43)	0.28(0.25-0.33)	0.001
X5 [(kPa/(L/s)]	-0.19(-0.25-(-0.17)	-0.13(-0.16-(-0.10)	0.0004
AX (kPa/L)	1.45±0.99	0.63±0.34	0.003
R5-R20 [(kPa/(L/s)]	0.13±0.08	0.06±0.03	0.0008
FEV_1 (% Predicted)	65(53-83)	101.0(88.55-110.4)	0.0001
FVC (% Predicted)	68(54-86)	102.2(95-107.2)	0.0001

R5: Respiratory system resistance at 5 Hz, R20: Respiratory system resistance at 20 Hz, X5: Respiratory system reactance at 5 Hz, AX: Area of reactance, FEV_1: Forced Expiratory Volume in 1st second, FVC: Forced Vital Capacity. Values given are either Mean±SD or Median (IQR). p value <0.05 is considered as significant.

Table 4. Reversibility of Impulse Oscillometry and Spirometric parameters in Sarcoidosis after inhalation of short acting bronchodilator

Parameters	Sarcoidosis (n=28) Pre bronchodilator	Sarcoidosis (n=28 Post bronchodilator	p value	% Change
R5 [(kPa/(L/s)]	0.55± 0.15	0.47± 0.11	0.0001	-12.62±11.97
X5 [(kPa/(L/s)]	-0.19(-0.26-(-0.17)	-0.15(-0.23-(-0.10)	0.0002	-0.22±0.11
R20 [(kPa/(L/s)]	0.37(0.32-0.50)	0.34(0.29-0.39)	0.0080	-10.22±19.62
X20 [(kPa/(L/s)]	-0.01±0.06	0.01±0.06	0.0015	5.62±235.6
AX (kPa/L)	1.31(0.86-2.37)	0.97(0.44-1.40)	0.0001	-33.05±24.88
R5-R20 [(kPa/(L/s)]	0.15±0.09	0.11± 0.08	0.0004	-27.59±73.24
FEV_1/FVC	77.34(72.56-82.75)	78.49(72.60-84.21)	0.6819	1.14±4.56
FEV_1 (% predicted)	64.79 ±21.08	63.46 ± 28.00	0.7293	6.07±7.27
FVC (% predicted)	70.89 ± 20.61	67.64 ± 27.22	0.4687	5.10±7.63
PEF (% predicted)	81.71±19.83	79.14±31.18	0.5239	2.53±11.97

R5: Respiratory system resistance at 5 Hz, R20: Respiratory system resistance at 20 Hz, X5: Respiratory system reactance at 5 Hz, X20: Respiratory system reactance at 20 Hz, AX: Area of reactance, FEV_1: Forced Expiratory Volume in 1st second, FVC: Forced Vital Capacity. Values given are either Mean±SD or Median (IQR). p value <0.05 is considered as significant.

Table 5. Correlation between Impulse Oscillometry and Spirometric parameters in Sarcoidosis patients (n=28)

Parameters	FEV_1 (% predicted)		FVC (% predicted)		FEV_1/FVC		PEF (% predicted)	
	r value	p Value	r value	p value	r value	p value	r value	p value
R5 [(kPa/(L/s)]	-0.53	0.004	-0.37	0.05	-0.37*	0.04	-0.49	0.008
X5 [(kPa/(L/s)]	0.72*	0.00001	0.61*	0.0005	0.20*	0.28	0.48*	0.01
R20 [(kPa/(L/s)]	-0.19*	0.332	-0.07*	0.69	-0.22*	0.24	-0.29*	0.12
AX (kPa/L)	-0.56*	0.002	-0.45*	0.01	-0.32*	0.09	-0.44*	0.01
R5-R20 [(kPa/(L/s)]	-0.56*	0.002	-0.48*	0.01	-0.30*	0.11	-0.48*	0.009
Fres (Hz)	-0.41	0.028	-0.28	0.14	-0.39*	0.03	-0.41	0.03

*R5: Respiratory system resistance at 5 Hz, R20: Respiratory system resistance at 20 Hz, X5: Respiratory system reactance at 5 Hz, AX: Area of reactance, F_{res}: Resonant frequency, FEV_1: Forced Expiratory Volume in 1st second, FVC: Forced Vital Capacity, PEF: Peak expiratory flow. r= Pearson / *Spearman correlation coefficient. P Value <0.05 is considered as significant*

Table 6. Receiver Operating Characteristic (ROC) curve analysis of Impulse Oscillometry parameters in Sarcoidosis

Parameters	Cut-off value	Sarcoidosis (n=28) vs Control (n=17)		Likelihood ratio	Area under curve (AUC)
		Sensitivity%	Specificity%		
R5 [(kPa/(L/s)]	≥ 0 .43	75.00	76.47	3.1875	0.8771
X5 [(kPa/(L/s)]	≥ -0.16	76.47	78.57	3.5686	0.8214
R20 [(kPa/(L/s)]	≥ 0 .33	71.43	76.47	3.0357	0.8267
X20 [(kPa/(L/s)]	≥ 0 .01	64.71	60.71	1.6471	0.7006
AX (kPa/L)	≥ 0 .91	71.43	70.59	2.4286	0.8046
R5-R20 [(kPa/(L/s)]	≥ 0 .1	71.43	76.47	3.0357	0.8403
Fres (Hz)	≥ 18.86	60.71	58.82	1.4745	0.6996

R5: Respiratory system resistance at 5 Hz, R20: Respiratory system resistance at 20 Hz, X5: Respiratory system reactance at 5 Hz, X20: Respiratory system reactance at 20 Hz, AX: Area of reactance, Fres: Resonant frequency

R5-R20 are most promising discriminating parameters with better sensitivity of 75.00%, 76.47% & 71.43% and specificity of 76.47%, 78.57% & 76.47% respectively. Detailed ROC curve analyses is given in the table 6.

Discussion

In sarcoidosis although parenchymal lung disease is more common, the airways (larynx, trachea and bronchi) may also get affected leading to airway obstruction (16). In the present study lung volumes, capacities and respiratory impedance were measured by using spirometry and impulse oscillometry respectively. The tests were performed before and 15 minutes after inhalation of short acting bronchodilator in patients with sarcoidosis and compared it with healthy controls.

Increased total as well as small airway resistance is observed in sarcoidosis. All the parameters which are suggestive of small airway resistance i.e. R5-R20, Ax and Fres (18) were increased in sarcoidosis. Also the sarcoidosis patients having post bronhodilator FEV_1/FVC ratio ≥ 70% which is cut off value for diagnosing Chronic Obstructive Pulmonary Diseases (21) had higher airway resistance as compared to controls. Tanizawa et al have compared spirometry and IOS parameters in sarcoidosis patients with and without hyper reactivity. They observed significantly increased R5 and R20 in patients showing hyper reactivity to inhaled methacholine while spirometry parameters were comparable between two groups (12). Thus as compared to spirometry, IOS is more sensitive and useful method for early detection of airway obstruction in sarcoidosis.

In spirometry, significantly reduced FEV_1, FVC and comparable FEV_1/ FVC was observed in sarcoidosis patients as compared to controls. Danila et. al. have compared the spirometric parameters in different radiographic stages of newly diagnosed sarcoidosis patient and reported normal pulmonary function tests in stage I and II while FEV_1 was reduced in stage III Sarcoidosis (9). Calaras et al have reported obstructive pattern (FEV_1/FVC<70%) in 9.7% patients while restrictive defects in 4.9% of sarcoidosis irrespective of staging (22).

Sarcoidosis is an inflammatory disorder characterized by presence of noncaseating granulomas at any organ or system but predominantly at intrathoracic lymphatic system and lungs. Pulmonary function test results are often normal in early stages but progressive impairment is seen in later stages of sarcoidosis. The most common pulmonary function abnormality in sarcoidosis is a restrictive pattern caused by pulmonary parenchymal involvement as the disease progresses in advance stage. But in many patients, concomitant obstructive impairment is also manifested by parenchymal infiltration which lead to airway distortion, peribronchial or peribrochiolar fibrosis. Bronchial distortion results in decreased expiratory flow rates. Sarcoidosis can affect the entire length of respiratory tract from upper airways to terminal bronchi (23,24). Involvement of distal airways by sarcoidosis may manifest as mucosal erythema, oedema, cobblestone mucosa, endobronchial granulomas, stenosis, extrinsic compression, distortion, bronchiectasis, bronchiolitis, airway hyper reactivity, and streaky hemoptysis. These can lead to airway dysfunction and respiratory symptoms. Sarcoid granulomas tend to develop along the broncho-vascular

bundle or in the vicinity of the airways. All of these changes are more likely to affect the airways in upper and mid-lung regions. Endobronchial involvement increases the risk of airflow limitation which can occur in up to 60% of sarcoid patients and can be seen in any stage (24).

R5 showed significant negative correlation with FEV_1, FEV_1/FVC and PEF. While R5-R20 and AX were significantly negatively correlated with FEV_1, FVC and PEF which suggest that as airway obstruction increases, airway resistance increases, and lung volumes, capacities and flow rate decreases. In the present study post bronchodilator reversibility of IOS parameters is demonstrated in sarcoidosis patients which suggests the potential role of bronchodilators in the management of especially early stages of sarcoidosis.

The small sample size is a major limitation of our study. More studies with a larger sample size can clarify this area in the future. The strength of the study includes a rigorous methodology for performance of spirometry and IOS procedures and analysis done.

Conclusion

Increased airway resistance is a better indicator of airway involvement than airflow limitation by spirometry in early stages of sarcoidosis.

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Author contributions: AT* and RG developed the concept behind the study. GB, AT*, NA, KM, and RG designed the study and enrolled subjects and acquired data. AT, AT*, NA and GB designed the analysis approach and performed the data analysis, interpretations and wrote the manuscript. All authors have read and approved the manuscript.

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