DOI: 10.7860/JCDR/2021/49633.15529

Original Article

Internal Medicine Section

Peripheral Arterial Disease as an Underdiagnosed Entity in COPD and its Impact on Functional Exercise Capacity- A Cross-sectional Study from a Tertiary Care Hospital in Eastern India

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ABSTRACT

Introduction: Chronic Obstructive Pulmonary Disease (COPD) is a significant cause of morbidity and mortality globally. COPD is a systemic disease, cardiovascular and Peripheral Arterial Disease (PAD) are common entities in COPD. Asymptomatic, undiagnosed PAD can lead to impaired functional exercise capacity, increased morbidity and mortality.

Aim: To find out the occurrence of PAD in COPD and relative contribution of PAD, severity of COPD, and Health Related Quality of Life (HRQL) on functional exercise capacity.

Materials and Methods: The present study was a prospective, cross-sectional, analytical study carried out in the Department of Respiratory Medicine of a teaching institution in eastern India over a period of six months. All COPD patients diagnosed as per Global Initiative for Obstructive Lung Diseases (GOLD) criteria were recruited for the study after obtaining written informed consent. HRQL was assessed by Clinical COPD Questionnaire (CCQ). Exercise capacity was assessed by Six Minute Walk Test (6MWT) and PAD was evaluated by Ankle Brachial Index (ABI) on Ultrasound (USG) Doppler. Data were analysed using appropriate statistical tests. Mean, Standard Deviation (SD) and percentages were calculated for descriptive frequencies, p-value was calculated using Fischer's-exact test or Chi-square test for categorical data and independent sample t-test and Kruskal Wallis test for parametric and non parametric data, respectively.

Results: Out of 75 COPD patients, PAD was present in 18 (24%) patients. Majority of COPD patients (n=35; 46.6%) were in GOLD group D. There was no statistically significant difference in age, Body Mass Index (BMI) and smoking index between COPD with and without PAD. Most PAD patients were asymptomatic. In comparison to COPD without PAD, severe PAD cases had significantly less Six Minute Walk Distance (6MWD), more episodes of leg cramps and needed to stop more frequently during 6MWT. Apart from PAD, increasing severity in COPD was associated statistically significant changes in Forced Expiratory Volume in the first second (FEV1), CCQ score, 6MWD, post 6MWT Heart Rate (HR), Respiratory Rate (RR), Borg score, fatigue, Oxygen Saturation (SpO_2).

Conclusion: The PAD is a frequent entity in COPD and can be diagnosed easily by measuring ABI. Increasing COPD severity affect HRQL and exercise capacity significantly.

Keywords: Ankle brachial index, Chronic obstructive pulmonary disease, Health-related quality of life, Six minute walk test

INTRODUCTION

The COPD is characterised by persistent airflow limitation. Exacerbations and systemic co-morbidities influence the course of COPD greatly [1]. COPD, being a systemic disease, is associated with several co-morbid conditions like cardiovascular diseases, atherosclerosis, PAD, depression, osteoporosis and others [1]. The 6MWT is now well accepted, validated and reliable test to assess the functional exercise capacity in patients with COPD. The 6MWD and postexercise dyspnea score also have prognostic implications, particularly in patients with severe COPD [2,3]. Whereas, HRQL questionnaire assesses patients' own perception of well-being, which may not corroborate with clinicians' assessment of disease severity and functional capacity of a particular patient. The occurrence of asymptomatic PAD among COPD patients has been reported to be quite high as compared to healthy smokers and non smokers, which has significant influence on the 6MWD [4,5]. A significant number of these underlying PAD may develop symptoms of claudication, rest pain leading to disability and complications like infections, limb gangrene and may require amputation [6,7]. So, early diagnosis and concomitant management of PAD is important for prevention of disability and better quality of life and outcome in these patients. Measurement of ABI by USG Doppler probe has evolved as a fairly sensitive non invasive tool for diagnosis of PAD [8].

Prevalence of PAD was found to be around 26.7% in a study done by Krishnan MN et al., in Kerala in Southern India [6]. Chakraborty D et al., from Tripura, India have shown that PAD was present in 29% of COPD patients in their study [7]. There is dearth of more robust information on relation between COPD and PAD from different parts of India. This study was undertaken with the primary objective of finding out occurrence of PAD in COPD and relative contribution of PAD, severity of COPD as per GOLD group, BMI, and perception of well-being on functional exercise capacity in stable COPD patients.

MATERIALS AND METHODS

A prospective, cross-sectional and analytical study of COPD patients attending Outpatient Department of Respiratory Medicine of a tertiary care teaching institution in eastern India. The study was conducted over a period of six months (July 2019-December 2019). It was approved by the Institutional Ethics Committee (Memo No. CMSDH/IEC/140/06-2019).

Case definition:

COPD: COPD is defined spirometrically as post bronchodilator FEV1/(Forced Vital Capacity (FVC)) value of <0.7 as per GOLD criteria [1].

PAD: ABI ≤0.90 remains the most common and consensual threshold for diagnosing PAD and is considered as cut-off value for diagnosing PAD in this study [8].

Inclusion criteria: The patients diagnosed as COPD as per GOLD criteria, irrespective of age and sex, attending chest Outpatient department of a tertiary hospital in a suburban area and those who gave written informed consent.

Exclusion criteria

- History of acute exacerbation (admitted in hospital for worsening of respiratory symptoms/attended Outpatient clinic or emergency department and were prescribed antibiotic with escalation of doses of inhalation medications) within last one month.
- COPD with cor pulmonale, pulmonary hypertension.
- Presence of associated co-morbid conditions like hypertension (systolic BP >140 mmHg and diastolic BP >90 mmHg), ischaemic heart disease, diabetes (fasting blood sugar> 126 mg/dL, PPBS >200 mg/dL), malignancy, neurological disorders.
- Diagnosed patients of peripheral vascular disease.
- Patients with severe osteoarthritis or who were using walking aids as these conditions will affect 6MWT.

Methods

- Diagnosis and assessment of COPD was done as per GOLD guideline [1].
- History of smoking (former/current/never) or environmental tobacco smoke. Smoking index was calculated as a product of number of cigarettes/bidi smoked per day and total number of years of smoking.
- BMI {weight(kg), height (cm)}
- Severity assessment– GOLD group A, B, C, or D {Modified Medical Research Council (MMRC) score, history of exacerbation/ hospitalisation} [1].
- GOLD stages- Stage 1, 2, 3, 4 based on spirometric value of post bronchodilator FEV1.
- Co-morbid illness- Diabetes (Fasting Blood Sugar (FBS), Glycated Haemoglobin (HbA1c)), Hypertension and Cardiovascular Disease (CVD) (Blood Pressure (BP) record, 12 lead Electrocardiogram (ECG), ±echocardiography, ±lipid profile).

HRQL

- Clinical COPD Questionnaire (CCQ) (version-, English or Hindi version)- It is a self-administered questionnaire specially developed to measure clinical control in patients with COPD. The questions were divided into three domains i.e., symptoms, functional and mental state (scale: 0=best, 6=worst) [9].

Calculation of scores: CCQ total score=(item 1+2+3+4+5+ 6+7+8+9+10)/10; Symptom=(item 1+2+5+6)/4; Functional state= (item 7+8+9+10)/4; Mental state=(item 3+4)/2.

- Modified Medical Research Council Dyspnea scale (MMRC)

As per MMRC scale severity of dyspnea is assessed on a scale of 0-4 (0-best; 4-worst) [10].

Functional exercise capacity:

- **6MWT-** (requirements-30 metres quiet hospital corridor, BORG score of dyspnea, measuring tape, digital finger pulse oximeter, stop watch, resting stool)- The patients recruited in the study was asked to walk in a 30 metres hospital corridor "as far as possible" in 6 minutes and instructed according to American Thoracic Society (ATS) guideline 2002 [11]. The distance covered in 6 min (6MWD), and post-test dyspnea score (BORG score) [12], pre and post-test HR, RR, capillary SpO_2, fatigue and episodes of leg cramps were recorded. For patients who needed to stop for sometimes during the 6MWT, number of such episodes and reason for stoppage (dyspnea or leg cramps or fatigue, etc.,) were also noted [11].

PAD: {USG machine with colour Doppler (Philips scanner HD7 was used in present study)}.

- History of presence, characteristics and severity of symptoms like claudication, risk for CVD, clinical examination.
- **Measurement of ABI by Doppler technique:** All patients were allowed a resting period of 10 minutes before measuring ABI. BP in the arm (systolic BP) was measured in the arm over brachial artery by using a random zero sphygmomanometer. For the legs, systolic BP of the posterior tibial artery and arteria dorsalis pedis were measured in both legs in supine position, cuff was tied one inch above medial malleolus. The colour filling pattern and flow direction was noted using linear probe in colour Doppler machine and finally spectral pattern was assessed to determine systolic BP. The ABI was defined as the ratio of highest systolic BP at the ankle to highest systolic BP at the arm and was calculated for each leg separately and lower ABI value was considered for the study. ABI was considered to be normal if it had a value > 0.9 and up to 1.40. The presence of PAD was defined as an ABI of 0.90 or less in at least one leg [8].
- **Interpretation of ABI [13,14]:** ABI ≤0.90 remains the most common and consensual threshold for diagnosing PAD. Based on PAD value, patients with PAD were further classified as following:

  - Mild PAD- 0.8<ABI≤0.9
  - Moderate PAD- 0.4<ABI≤0.8.
  - Severe PAD- ABI≤0.4
- Abnormally high ABI– ABI above 1.3 may be due to arterial wall calcification in disease conditions like medial calcinosis, diabetes, end-stage renal disease. ABI is not helpful in detecting occlusive disease. In this condition Toe-Brachial Index (TBI) was used in this scenario because digital vessels rarely develop calcification and TBI value <0.6 was considered abnormal [15,16].

STATISTICAL ANALYSIS

Statistical analysis was performed using Statistical Package for the Social Sciences (SPSS) version 20.0 (SPSS inc. Chicago, IL) software for MS-Windows. Descriptive statistics were expressed using Mean and Standard Deviation (Mean±SD) for numerical variables and percentage for categorical variable. The normality of the data were tested with Shapiro-Wilk test. Difference between groups was calculated using Fisher's-exact test or Chi-square test for categorical variables. Difference of numerical variables between more than two groups were estimated using Kruskal Wallis test when the data was non parametric. Post hoc analysis was done for pairwise comparison of groups following Kruskal Wallis test. Independent samples t-test was used for comparing two groups with parametric data. The p-value of <0.05 was considered significant.

RESULTS

A total of 75 COPD patients were considered for the study. 18 out of 75 (24%) COPD patients were found to have PAD. Out of these 18 COPD patients with PAD, 10 patients (55.6%) had mild PAD, 4 patients (22.2%) had moderate PAD and 4 patients (22.2%) had severe PAD.

Mean age of the study group was 62.09±9.148 years (Mean±SD). There was no significant difference in age distribution between COPD patients with PAD and COPD patients without PAD [Table/ Fig-1]. There was clear male predominance with 68 out of 75 (90.7%) being male. Smoking index was similar in both COPD with PAD and COPD without PAD. There was no significant difference in CCQ score between patients with PAD and without PAD. Overall, mean FEV1 was 1.15±0.45 L with no significant difference between patients with PAD and those without PAD [Table/Fig-1].

On further analysis of GOLD groups, there was no appreciable difference in age and sex distribution, smoking index, BMI between

Variables	COPD with PAD (n=18)	COPD without PAD (n=57)	p-value (Independent samples t test)
Age (years) (mean±SD)	62.11±9.35	62.09±9.17	0.99
Sex (M:F)	17:1	51:6	
BMI (kg/m^2) (mean±SD)	19.22±3.64	20.15±4.04	0.39
Smoking Index (mean±SD)	521.94±285.81	649.16±608.76	0.396
CCQ Score (mean±SD)	23.61±8.85	21.44±7.29	0.296
FEV1 (L) (mean±SD)	1.21±0.56	1.13±0.42	0.52

[Table/Fig-1]: Demographic profile.
*BMI: Body mass index; CCQ: Clinical COPD questionnaire; FEV1: Forced expiratory volume in 1 second

different COPD groups (A-B-C-D). On the other hand, statistically significant differences were noted among different GOLD groups in terms of FEV1, CCQ score, 6MWD, post 6MWT HR, post 6MWT RR, post 6MWT SpO_2, post Borg score, post 6MWT fatigue score [Table/Fig-2]. In addition to this there was a statistically significant difference in MMRC score among GOLD groups (p<0.0001).

Variables	Overall (n=75)	GOLD Group A (n=17)	GOLD Group B (n=17)	GOLD Group C (n=6)	GOLD Group D (n=35)	p-value (Kruskal Wallis test)
BMI (kg/m^2) (mean±SD)	19.92± 3.95	20.01± 3.23	19.95± 3.85	20.14± 2.91	20.02± 4.33	0.681
Smoking Index (mean±SD)	604.71± 552.71	607.79± 771.59	602.13± 402.89	594.28± 600.41	606.84± 404.30	0.257
CCQ Score (mean±SD)	21.96± 7.69	14.82± 4.55	23.18± 6.002	16.17± 2.99	25.83± 2.89	<0.0001
FEV1 (L) (mean±SD)	1.15± 0.45	1.55± 0.41	1.28± 0.34	1.14± 0.21	0.87± 0.31	<0.0001
6MWD (metre) (mean±SD)	420.99± 84.33	475.45± 67.20	433.11± 55.46	451.50± 58.38	383.41± 90.71	0.003
Post 6MWT HR (mean±SD) (beats/min)	105.07± 17.7	91.65± 10.93	108.59± 17.36	108± 22.08	109.37± 17.18	0.003
Post 6MWT RR (mean±SD) (breaths/min)	28.81± 5.05	25.24± 3.35	28.71± 4.70	30± 4.20	30.40± 5.29	0.005
Post 6MWT SpO_2 (mean±SD) (%)	95.73± 3.63	96.94± 1.71	96.94± 1.75	96.67± 2.50	94.11± 4.64	0.015
Post 6MWT Borg Score (mean±SD)	2.107± 1.63	0.53± 0.59	2.35± 0.79	2.17± 1.47	2.74± 1.82	<0.0001
Post 6MWT Fatigue (mean±SD)	0.95± 1.60	0.12± 0.47	1.5± 1.31	0.92± 0.75	1.3± 1.95	0.005

[Table/Fig-2]: GOLD group-wise comparison of BMI, FEV1, CCQ score and functional exercise capacity.
*BMI: Body mass index; CCQ: Clinical COPD questionnaire; FEV1: Forced expiratory volume in 1 second; 6MWT: Six minute walk test; 6MWD: Six minute walk distance

On further post-hoc analysis for pairwise comparison of groups, there was significant difference in FEV1 between GOLD group D and B and GOLD group D and A [Table/Fig-3]. As regard to CCQ score specific difference were noted between GOLD group A and B, GOLD group A and D and GOLD group C and D [Table/Fig-3]. On analysing 6MWD, significant difference was noted between GOLD group A and D only [Table/Fig-3]. Similarly, differences in post 6MWT fatigue score was mainly found between GOLD groups A and B. As for post 6MWT Borg score differences were prominent among GOLD group A and B, and also GOLD group A and D [Table/Fig-3]. In addition to this, differences in post 6MWT RR was mainly found between GOLD group A and D; whereas significant differences were demonstrated in post 6MWT HR among GOLD group A and B and GOLD group A and D.

Variables	GOLD group	GOLD group	p-value**
FEV1 (L)	Group B	Group D	0.008
	1.28±0.34	0.87±0.31	
	Group A	Group D	<0.0001
	1.55±0.41	0.87±0.31	
CCQ Score	Group A	Group B	0.003
	14.82±4.55	23.18±6.002	
	Group A	Group D	<0.0001
	14.82±4.55	25.83±2.89	
	Group C	Group D	0.012
	16.17±2.99	25.83±2.89	
6MWD (metre)	Group A	Group D	0.002
	475.45±67.20	383.41±90.71	
Post 6MWT borg score	Group A	Group B	0.001
	0.53±0.59	2.35±0.79	
	Group A	Group D	<0.0001
	0.53±0.59	2.74±1.82	
Post 6MWT fatigue	Group A	Group B	0.004
	0.12±0.47	1.5±1.31	

[Table/Fig-3]: Post-hoc analysis of comparison between GOLD groups.
* CCQ: Clinical COPD questionnaire; FEV1: Forced expiratory volume in 1 second; 6MWT: Six minute walk test; 6MWD: Six minute walk distance
**Independent samples t-test was used

No statistically significant relation was found between severity of COPD (as per GOLD group ABCD) and occurrence and severity of PAD- out of a total of 18 PAD patients, eight patients belonged in GOLD group D. So, 44.4% patients of COPD with PAD belonged to Gold group D, and 57.9% patients in COPD without PAD group also belonged to GOLD group C or D [Table/Fig-4]. However, 70% of mild PAD (n=10) cases were in GOLD group A or B, whereas 62.5% of moderate to severe PAD (n=8) cases were found to be in GOLD group D, but this was not statistically significant in this study.

PAD	GOLD Group A (n=17)	GOLD Group B (n=17)	GOLD Group C (n=6)	GOLD Group D (n=35)	Total
Present	5	5	0	8	18
Absent	12	12	6	27	57
Total	17	17	6	35	75

[Table/Fig-4]: Distribution of PAD among different GOLD groups.
*GOLD: Global initiative for obstructive lung diseases; PAD: Peripheral arterial disease

There was no statistically significant difference in mean ABI value among GOLD groups (A-B-C-D) (p-0.606). Mean 6MWD was 412.61±86.50 metre in COPD with PAD, and 423.63±84.24 metre in COPD without PAD and the difference was not statistically significant, but patients with severe PAD had significantly lower 6MWD value (327.32±84.99 metre) compared to mild PAD (416.92±77.77 metre) and patients without PAD (423.63±84.24 metre) [Table/Fig-5]. There was no significant difference in post 6MWD, HR, RR, SpO_2, dyspnea in Borg scale and fatigue between patients with and without PAD. However, patients with moderate

Exercise capacity	COPD with moderate to severe PAD (n=8)	COPD without PAD (n=57)	p-value (Independent samples t-test)
6MWD (metre) (mean±SD)	327.32±84.99	423.63±84.24	0.0036
Leg cramps	4	9	0.04
No. of people needed to halt during 6MWT	4	5	0.01
Total no. of halts during walking 6MWT	12	9	0.0001

[Table/Fig-5]: Exercise capacity in COPD with moderate and severe PAD vs without PAD.
*6MWT: Six minute walk test; 6MWD: Six minute walk distance

to severe PAD had significantly more episodes of leg cramp and need to stop more frequently during 6MWT compared to patients without PAD [Table/Fig-5].

DISCUSSION

The PAD is found to be a common accompaniment in COPD across the world. The purpose of this study was to estimate occurrence of PAD in stable COPD patients. In this study, 24% (n=18) of COPD patients were found to have PAD, and of this PAD cases 55.6% (n=10) cases were mild PAD, and 22.2% (n=4) cases were in moderate and severe PAD group each. Similar occurrence of PAD in COPD have been reported in two previously published Indian studies by Krishnan MN et al., (26.7%) and Chakraborty D et al., (29%) [6,7]. Houben-Wilke S et al., have reported a figure of 8.8% PAD cases in COPD in their COSYCONET study [17], but literatures across the world have reported a wide range of 8-81% occurrence of PAD in COPD [Table/Fig-6] [4,5,7,17-22]. There was no statistically significant difference noted between COPD with PAD and COPD without PAD in relation to age, sex, smoking index, BMI, CCQ score and FEV1 in this study. Terzikhan N et al., and Jonathon T et al., have also reported the same findings [18,23]. However, Matsuoka H et al., have found significant correlation of ABI with age, FEV1, smoking pack-years, MMRC dyspnea scale and resting SpO_2 [21]. Seven out of ten (70%) mild PAD cases belonged to GOLD A or B, on the other hand five out eight (62.5%) of moderate and severe PAD cases belonged to GOLD group D in this study, but this was not found to be statistically significant (p-value-0.34). However, in the COSYCONET study PAD was more frequent in patients with increasing severity as per GOLD stage- PAD was present in 5.1%, 7.4%, 11.1%, and 9.5% in GOLD stage 1,2, 3 and 4, respectively [17]. Four out of 18 (22.2%) patients with PAD had complaints of leg cramp and had to stop for sometimes during 6MWT and all of them belonged to moderate to severe PAD, rest 77.8% patients with PAD including all mild cases were able to complete 6MWT uninterrupted. Other studies have also reported that majority of PAD patients don't exhibit any symptoms, it has been reported in two other studies that only 21.4% and 33% of PAD patients had symptoms suggestive of PAD in their respective studies [18,24]. Pecci R et al., has also noted that 70.9% PAD patients were asymptomatic in their study [5]. Hooi JD et al., have shown that increased cardiovascular morbidity {Hazard Ratio (HR) 1.6, 95% Confidence Interval (CI) 1.3-2.1}, cardiovascular mortality (HR 1.5, 95% CI 1.1-2.1) and total mortality (HR 1.4, 95% CI 1.1-1.8) were significantly associated even with asymptomatic PAD [25]. An increased risk of mortality has also been reported in this asymptomatic PAD group by Terzikhan N et al., and Diehm C et al., too in their studies with adjusted HR of 1.4 in both the studies [18,26]. McDermott MM et al., have observed that impaired 6MWD, walking speed and standing balance was seen in patients with asymptomatic PAD [27]. Moreover, many of these asymptomatic and undiagnosed PAD patients fall into Fontaine class III and IV as per Fontaine Classification of PAD suggesting that they have critical limb ischaemia implying end-stage PAD [28,29]. Later, some of them developed rest pain and ulcerative gangrene [28,29]. These facts emphasise and reinstate the need for an early diagnosis of PAD in COPD patients.

In the present study, severe PAD patients had statistically significant difference in 6MWD, leg cramps and need for stoppage during 6MWT. Results of COSYCONET study has demonstrated a significant impairment in functional exercise capacity as evidenced by a low 6MWD in PAD group (356 metres vs 422 metres) [17].

Most of the COPD patients belonged to GOLD group D in this study (46.6%) and majority were male and smoker but no significant differences were found among different GOLD groups in terms of smoking index and BMI. A significant change was observed with increasing severity of COPD groups in relation to FEV1, CCQ score and MMRC score, 6MWD, and most of the post 6MWT parameters like post HR, post RR, post Borg score, fatigue, post SpO_2. On post hoc analysis of pairwise comparison among GOLD groups, most of these differences were more significantly noted among GOLD group A with GOLD group D and B or between GOLD group B and D. Agarwal SR et al., also concluded in their study that severity assessment according to GOLD guidelines more significantly correspond to changes in HRQL and functional exercise capacity (6MWD) in patients having higher stages of COPD than in lower stages [30].

Author	Country and sample size	Criteria for diagnosis of PAD	Prevalence (%)
Houben-Wilke S et al., [17]	Germany (n=2088)	ABI <0.9	8.8
Terzikhan N et al., [18]	Netherland (n=3123)	ABI<0.9	12.9
Castagna O et al., [4]	France (n=151)	ABI<0.9	81.4
Blum A et al., [19]	Israel (n=87)	ABI<0.9	31
Pecci R et al., [5]	Spain (n=246)	ABI<0.9	36.8
Lin MS et al., [20]	Taiwan (n=427)	ABI<0.9	8
Matsuoka H et al., [21]	Japan (n=55)	ABI<0.9	9.8
Sun KS et al., [22]	Taiwan (n=200)	ABI<0.9	8.5
Chakraborty D et al., [7]	India (n=115)	ABI<0.9	29.57
Mukherjee S et al., (Present study)	India (n=75)	ABI <0.9	24

[Table/Fig-6]: Prevalence of PAD in COPD in other studies [4,5,7,17-22].

Limitation(s)

Limitation of present study was that there was less number of severe PAD cases in present study which may be the reason behind not being able to elicit statistically significant comparison among different categories of PAD severity. A longitudinal multicentric study comprising of larger sample size will be better in future.

CONCLUSION(S)

The PAD is a common entity in COPD and should be looked for in all cases of COPD. Most PAD are asymptomatic and only a proportion of severe PAD patients become symptomatic. ABI is a sensitive and easy tool for early diagnosis of PAD in COPD patients and should be resorted to in all COPD patients to prevent increased morbidity and mortality risk due to PAD.

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PLAGIARISM CHECKING METHODS: [Jain H et al.]
- Plagiarism X-checker: Apr 09, 2021
- Manual Googling: Aug 16, 2021
- iThenticate Software: Sep 15, 2021 (15%)

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. No

Date of Submission: **Apr 08, 2021**
Date of Peer Review: **Jul 14, 2021**
Date of Acceptance: **Aug 17, 2021**
Date of Publishing: **Oct 01, 2021**