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# Correlation between pulmonary function tests and carotid intima-media thickness in patients with chronic obstructive pulmonary disease - A hospital-based cross-sectional study

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## Abstract

**Background:** Chronic obstructive pulmonary disease (COPD) carries excess cardiovascular morbidity and mortality that is not explained by conventional vascular risk factors. Carotid intima-media thickness (CIMT) is a validated non-invasive marker of subclinical atherosclerosis, but data relating airflow limitation to CIMT in patients free of classical risk factors are limited.

**Methods:** Fifty consecutive patients aged 18 years or above with spirometry - confirmed COPD (post-bronchodilator FEV1/FVC below 0.70) were enrolled in a hospital-based cross-sectional study at a tertiary care teaching hospital in Bengaluru. Patients with diabetes mellitus, hypertension, ischaemic heart disease, cerebro vascular disease, other chronic lung disease, or those on anti-platelet, anticoagulant or statin therapy were excluded. All underwent spirometry and B-mode Ultrasonography measurement of CIMT. Analysis of variance, chi-square test, Pearson correlation and receiver operating characteristic analysis were used.

**Results:** Mean age was 62 ± 10 years and 40 patients (80%) were male. Airflow limitation was mild in 16 (32%), moderate in 26 (52%), severe in 6 (12%) and very severe in 2 (4%). Mean CIMT rose stepwise across these grades at 0.90 ± 0.16, 1.13 ± 0.26, 1.60 ± 0.14 and 1.95 ± 0.07 mm ($p < 0.001$). CIMT correlated inversely with FEV1 ($r = -0.557$, $p < 0.001$), FVC ($r = -0.389$, $p = 0.005$) and FEV1/FVC ($r = -0.703$, $p < 0.001$), but not with age ($r = -0.095$, $p = 0.510$). CIMT predicted in-hospital mortality with an area under the curve of 0.940; a cut-off above 1.4 mm gave 85.7% sensitivity and 94.4% specificity.

**Conclusion:** CIMT increases in proportion to the severity of airflow limitation in COPD independent of

traditional vascular risk factors, supporting carotid Ultrasonography as a simple screening tool in this population.

**Keywords:** Atherosclerosis, Carotid Intima-Media Thickness, Chronic Obstructive Pulmonary Disease, Forced Expiratory Volume, Spirometry, Subclinical Cardiovascular Disease.

**Introduction**

Chronic obstructive pulmonary disease (COPD) is one of the largest contributors to chronic respiratory morbidity and premature death worldwide. The 2023 Global Initiative for Chronic Obstructive Lung Disease (GOLD) report defines COPD as a heterogeneous lung condition characterised by chronic respiratory symptoms such as dyspnoea, cough, sputum production and exacerbations, arising from abnormalities of the airways or alveoli that produce persistent and often progressive airflow obstruction.[1] This revised definition deliberately moves the emphasis away from a single spirometric threshold and towards the biological and clinical heterogeneity of the disease, and it is accompanied by a proposed taxonomy of aetiotypes that recognises tobacco smoke, biomass exposure, occupational exposures, early life events and genetic susceptibility as distinct pathways to a common physiological end point.[1,2] In India the disease burden is disproportionately high because of the combined effect of tobacco use, indoor biomass fuel combustion, ambient air pollution, recurrent childhood respiratory infection and undernutrition, and a substantial proportion of patients present for the first time only when airflow obstruction is already advanced or when an acute exacerbation forces hospital admission.

The pathological substrate of COPD is an amplified inflammatory response of the airways and lung parenchyma to inhaled noxious particles and gases, with neutrophils, macrophages and CD8 positive lymphocytes accumulating in the small airways, protease and antiprotease imbalance, oxidative stress, apoptosis of alveolar septal cells and ineffective repair.[3]

The functional consequences are small airway narrowing, loss of elastic recoil, expiratory flow limitation, air trapping and hyperinflation. Spirometry remains the objective foundation of diagnosis: a post-bronchodilator ratio of forced expiratory volume in one second to forced vital capacity (FEV1/FVC) below 0.70 confirms persistent airflow obstruction, while the percentage predicted FEV1 grades its severity.[2] Spirometry also carries prognostic weight, since a falling FEV1 tracks with symptom burden, exacerbation frequency, hospitalisation and death, and forms one component of composite prognostic indices such as the body mass index, airflow obstruction, dyspnoea and exercise capacity index.[4]

It is now clearly established that COPD is not confined to the lung. Systemic manifestations including skeletal muscle dysfunction, weight loss, osteoporosis, anaemia, depression and cardiovascular disease materially influence outcome, and cardiovascular disease is among the commonest and most lethal comorbidities. A systematic review of cardiovascular comorbidity in COPD found consistently higher prevalence of ischaemic heart disease, heart failure, arrhythmia and peripheral vascular disease in patients with COPD than in matched controls, with cardiovascular events accounting for a large share of hospitalisations and deaths, particularly in those with mild to moderate airflow obstruction who are least likely to die of respiratory failure.[5]

Reported prevalence of cardiovascular disease in COPD cohorts ranges widely, from roughly a quarter to more

than two thirds of patients depending on case definition and the intensity of screening.[5,6]

The epidemiological link between impaired lung function and vascular events is robust and graded. A population-based analysis together with a systematic review of the literature showed that a reduction in FEV1 is an independent predictor of cardiovascular mortality, with a decrement of approximately 10% in percentage predicted FEV1 associated with a clinically meaningful increase in cardiovascular death, an association that persists after adjustment for age, sex and smoking history.[7] Because smoking is a shared exposure, the central question has been whether reduced lung function is merely a marker of cumulative tobacco exposure or whether the inflammatory and hypoxaemic milieu of COPD itself accelerates atherogenesis. Evidence favouring the latter includes the observation that airflow limitation predicts vascular disease in never smokers and in ex-smokers, and that markers of systemic inflammation rise in parallel with the severity of obstruction.[6,7]

Several biologically plausible mechanisms have been proposed. Chronic low grade systemic inflammation, reflected in elevated C-reactive protein, fibrinogen, interleukin-6 and tumour necrosis factor alpha, promotes endothelial activation, monocyte recruitment, foam cell formation and plaque instability.[8] Oxidative stress generated both by inhaled smoke and by activated inflammatory cells reduces nitric oxide bioavailability and impairs endothelium-dependent vasodilatation. Intermittent and sustained hypoxaemia, hypercapnia, sympathetic activation, increased arterial stiffness and repeated exacerbations, each of which is accompanied by a surge in inflammatory mediators and a transient prothrombotic state, provide additional pathways.[8,9] Accelerated vascular ageing, shared genetic susceptibility and physical inactivity secondary to dyspnoea complete a picture in which the lung and the arterial wall are affected by a common process rather than by two independent diseases.

Detecting this vascular involvement before an event occurs is clinically attractive but technically demanding. Conventional office-based risk scores perform poorly in patients whose dominant risk factor is a chronic inflammatory lung disease, and stress testing is frequently uninterpretable in COPD because exertional dyspnoea limits exercise duration and hyperinflation degrades echocardiographic windows. Carotid intima-media thickness measured by high resolution B-mode ultrasonography circumvents these problems. It is inexpensive, reproducible, free of ionising radiation and repeatable, and it quantifies the combined thickness of the intimal and medial layers of the arterial wall as the distance between the lumen-intima and media-adventitia interfaces, most reliably at the far wall of the distal common carotid artery.[10] Values above the seventy fifth percentile for age, sex and ethnicity, or an absolute thickness exceeding 1.0 mm, are conventionally regarded as abnormal, while focal thickening beyond 1.5 mm defines plaque.[10] The prognostic credentials of CIMT are well documented in general populations. In the Cardiovascular Health Study, increased CIMT was associated with a stepwise rise in the risk of incident myocardial infarction and stroke among older adults free of clinical cardiovascular disease at baseline.[11] Subsequent analyses of the Framingham Offspring cohort confirmed that carotid wall thickness, and particularly internal carotid measurements, adds incremental predictive information to standard risk factors and improves reclassification of intermediate risk

individuals.[12] The Atherosclerosis Risk in Communities study established the association between carotid wall thickness and incident coronary heart disease, and demonstrated that impaired lung function is itself associated with subclinical carotid atherosclerosis.[13] These observations have translated into guideline recognition of carotid ultrasonography as a reasonable adjunct for cardiovascular risk assessment in selected asymptomatic adults.

Studies focused specifically on COPD have converged on the same conclusion. Iwamoto and colleagues showed in middle-aged men that smokers with airflow limitation had significantly greater CIMT than control smokers and never smokers, indicating that atherosclerotic change begins early in the natural history of COPD and is not attributable to smoking alone.[14] Among 585 patients undergoing vascular surgery, van Gestel and co-workers found that COPD was independently associated with increased carotid wall thickness after adjustment for age and smoking status, and that increased thickness predicted total and cardiovascular mortality.[15] In the Rotterdam Study, participants with COPD had a higher prevalence of carotid wall thickening and, on magnetic resonance imaging, a greater frequency of lipid core containing vulnerable plaque than participants with normal lung function.[16] Analyses from the MESA Lung Study similarly linked airflow obstruction and emphysema to subclinical atherosclerosis.[17] A meta-analysis of literature studies pooling several thousand patients and controls confirmed that CIMT and the prevalence of carotid plaque are significantly greater in COPD than in comparison groups.[18]

Indian data, although fewer, point in the same direction. A prospective hospital-based case-control study from northern India reported carotid plaque in 38.7% of 142 patients with COPD compared with 13.7% of controls, and concluded that carotid screening should form part of cardiovascular assessment in COPD.[19] Nevertheless, important gaps persist. Most published work is case-control in design and recruits patients who also carry diabetes mellitus, hypertension, dyslipidaemia or established coronary disease, or who are already receiving statins and antiplatelet agents, all of which independently modify carotid wall thickness and therefore confound the relationship of interest. Comparatively few studies have examined a cohort deliberately stripped of these classical risk factors in order to isolate the contribution of airflow limitation itself, and fewer still have quantified the relationship as a continuous correlation between spirometric indices and CIMT rather than as a categorical comparison between disease and health. In addition, most reports describe stable outpatients, whereas a large proportion of patients with COPD in Indian public hospitals are first evaluated during an acute exacerbation, a physiological state in which inflammatory activation and hypoxaemia are maximal and in which the vascular phenotype of the disease may be most readily demonstrated. The behaviour of carotid wall thickness across GOLD grades in such an exacerbation cohort has been little studied.

Clarifying this relationship has practical value in resource-constrained settings. Spirometry is increasingly available at district level in India, whereas carotid Doppler Ultrasonography and cardiology referral are concentrated in tertiary centers. If the degree of airflow limitation reliably predicts carotid wall thickness, then a simple spirometric measurement could be used to identify the subgroup of patients with COPD in whom carotid imaging, aggressive risk factor modification, smoking cessation support and pulmonary rehabilitation

would yield the greatest cardiovascular benefit. Conversely, if CIMT is elevated even in patients with mild obstruction, this would argue for vascular assessment early in the disease course rather than after symptoms of coronary or cerebrovascular disease appear.

The present study was therefore designed to measure CIMT in patients with spirometry-confirmed COPD who were free of diabetes mellitus, hypertension, ischaemic heart disease, cerebrovascular disease and vasoactive drug therapy, and to examine the correlation between pulmonary function indices and carotid wall thickness across the spectrum of GOLD severity grades in a tertiary care teaching hospital population in southern India.

**Aims and Objectives**

1. To measure carotid intima-media thickness by B-mode Ultrasonography in patients with chronic obstructive pulmonary disease.
2. To correlate pulmonary function test indices, namely FEV1, FVC and the FEV1/FVC ratio, with carotid intima-media thickness in patients with chronic obstructive pulmonary disease.
3. To describe the distribution of carotid intima-media thickness across GOLD grades of airflow limitation severity and to explore its relationship with in-hospital outcome.

**Materials and Methods**

**Study design and setting**

This was a hospital-based, observational, cross-sectional study carried out in the Department of General Medicine at hospitals attached to Bangalore Medical College and Research Institute, Bengaluru, a tertiary care teaching institution in southern India. Patients were recruited from both the outpatient department and the inpatient wards over a period of nineteen months, from February 2021 to August 2022.

**Study population and sample size**

The sample size was calculated using the standard formula for estimation of a mean in a cross-sectional design, $n = Z^2\sigma^2/d^2$, where Z was the standard normal deviate for a 95% confidence interval (1.96), σ was the standard deviation of carotid intima-media thickness taken as 0.35 mm from a previously published Indian study of carotid wall thickness in COPD, and d was the absolute precision of 0.1 mm. Substitution yielded a minimum requirement of 47 participants, which was rounded up to 50. Fifty consecutive patients satisfying the eligibility criteria were therefore enrolled.

**Inclusion criteria**

Patients aged 18 years or above, with a diagnosis of COPD established according to the GOLD 2019 diagnostic criteria and confirmed by a post-bronchodilator FEV1/FVC ratio below 0.70, and who were willing to provide written informed consent, were included.

**Exclusion criteria**

Patients were excluded if they were unwilling to give informed consent; had chronic lung disease other than COPD such as bronchial asthma, bronchiectasis, interstitial lung disease or pulmonary tuberculosis with significant sequelae; had type 2 diabetes mellitus; had systemic hypertension; had undergone previous coronary revascularisation or carotid artery surgery; had documented cerebrovascular disease; had ischaemic heart disease or acute coronary syndrome; or were receiving anticoagulant, antiplatelet or statin therapy. These exclusions were applied deliberately so that the observed relationship between airflow limitation and carotid wall thickness would not be confounded by

established atherosclerotic risk factors or by drugs known to modify intima-media thickness.

**Clinical assessment**

After enrolment, a detailed history was recorded on a predesigned proforma covering the duration and pattern of respiratory symptoms, smoking history in pack years, exposure to biomass fuel and occupational dusts, alcohol intake, the number of exacerbations in the preceding year and the presence of an exacerbation at the time of assessment. Breathlessness was graded using the modified Medical Research Council (mMRC) dyspnoea scale from 0 to 4. A complete general physical and systemic examination was performed, with specific documentation of pallor, cyanosis, clubbing, pedal oedema, jugular venous pressure, pulse rate, blood pressure, respiratory rate and peripheral oxygen saturation. Height and weight were recorded and body mass index calculated as weight in kilograms divided by height in metres squared. The extended Medical Research Council dyspnoea (eMRCD) score was also documented.

**Pulmonary function testing**

Spirometrywas performed in all patients by a trained technician using a calibrated spirometer, in accordance with American Thoracic Society and European Respiratory Society acceptability and repeatability standards. Measurements were obtained before and fifteen minutes after inhalation of a short-acting bronchodilator, and the best of three technically acceptable manoeuvres was recorded. FEV1 and FVC were expressed as percentages of predicted values for age, sex and height, and the FEV1/FVC ratio was calculated. A post-bronchodilator FEV1/FVC below 0.70 confirmed persistent airflow obstruction, and the severity of airflow limitation was graded according to the GOLD 2019 classification as mild (FEV1 at or above 80% predicted), moderate (50% to less than 80%), severe (30% to less than 50%) and very severe (below 30% predicted).

**Measurement of carotid intima-media thickness**

Carotid intima-media thickness was measured by B-mode ultrasonography using a high frequency linear array transducer with the patient supine, the neck slightly extended and the head rotated away from the side being examined. The common carotid artery, the bifurcation and the proximal internal carotid artery were examined bilaterally. Intima-media thickness was taken as the distance between the leading edge of the lumen-intima interface and the leading edge of the media-adventitia interface of the far wall of the distal common carotid artery, measured in a plaque-free segment approximately one centimetre proximal to the bifurcation. Measurements were obtained at end diastole in three separate planes on each side and the mean of the readings was used for analysis. All studies were performed by an experienced radiologist blinded to the spirometric grade.

**Laboratory investigations**

Venous blood was drawn at admission for complete haemogram including haemoglobin, total leucocyte count, differential count and platelet count; renal function tests comprising blood urea, serum creatinine and serum uric acid; liver function tests comprising total and direct bilirubin, total protein, serum albumin, prothrombin time and international normalised ratio; serum electrolytes; and random blood sugar. A twelve-lead electrocardiogram and a chest radiograph were obtained in all patients. Eosinopeniawas defined as an absolute eosinophil count below the laboratory reference

range. Arterial blood gas analysis was performed where clinically indicated.

**Ethical considerations**

The study protocol was approved by the Institutional Ethics Committee of Bangalore Medical College and Research Institute before commencement of recruitment. Written informed consent was obtained from every participant in the language best understood by the patient, using consent documents available in English, Kannada and Hindi. Participants were informed of their right to withdraw at any stage without prejudice to their treatment, and patient identifiers were removed before analysis.

**Statistical analysis**

Data were entered into a Microsoft Excel spreadsheet and analysed using the Statistical Package for the Social Sciences version 20 (IBM Corp., Armonk, NY, USA). Continuous variables were summarised as mean and standard deviation and categorical variables as frequencies and percentages. Comparison of continuous variables across the four GOLD grades was performed using one-way analysis of variance, and categorical variables were compared using the chi-square test or Fisher exact test as appropriate. The relationship between carotid intima-media thickness and continuous spirometric variables was assessed using the Pearson correlation coefficient. Receiver operating characteristic curve analysis was used to evaluate the discriminatory ability of carotid intima-media thickness for in-hospital mortality, with the optimal cut-off identified by the Youden index. A two-tailed p value below 0.05 was considered statistically significant.

**Results**

Fifty patients with spirometry-confirmed COPD were studied. The mean age of the cohort was 62 ± 10 years, with a range of 42 to 81 years, and 40 patients (80%) were male. Airflow limitation was mild in 16 patients (32%), moderate in 26 (52%), severe in 6 (12%) and very severe in 2 (4%), so that 32 patients (64%) fell into the severe or moderate categories combined. All 50 patients (100%) were assessed during an exacerbation and all had acidaemia on blood gas analysis at presentation.

Baseline demographic and clinical characteristics stratified by GOLD grade are presented in Table 1. Mean age was almost identical across grades at 62 ± 8, 62 ± 11, 62 ± 10 and 59 ± 19 years for mild, moderate, severe and very severe disease respectively (p = 0.963). Body mass index declined progressively from 23.7 ± 3.4 kg/m² in mild disease to 23.1 ± 4.9, 21.5 ± 1.8 and 20.5 ± 0.9 kg/m² in moderate, severe and very severe disease, but this gradient did not reach statistical significance (p = 0.583). Male preponderance increased with severity, from 10 of 16 patients (62.5%) in the mild group to all 6 patients (100%) in the severe group, without attaining significance (p = 0.077). Thirty-seven patients (74%) were smokers, and the proportion of smokers was 56.3% in mild, 84.6% in moderate and 83.3% in severe disease (p = 0.171). Eighteen patients (36%) consumed alcohol (p = 0.663). Breathlessness alone was the presenting complaint in 15 patients (30%), breathlessness with cough in 20 (40%) and breathlessness with cough and either chest pain or wheeze in 15 (30%), with no significant difference across grades (p = 0.234). The distribution of Mmrcdyspnoea grades differed significantly across GOLD grades (p = 0.042); 33 patients (66%) had an mMRC grade of 2 or more, and both patients with very severe disease had an mMRC grade of 3 or 4. Pedal oedema was present in 11 patients (22%) and was not associated with severity (p = 0.770),

while cyanosis and elevated jugular venous pressure were absent in all patients and the electrocardiogram was normal in all patients.

Table 1: Baseline demographic and clinical characteristics by GOLD grade of airflow limitation (n = 50)

| Variable | Mild (n=16) | Moderate (n=26) | Severe (n=6) | Very severe (n=2) | p value |
|---|---|---|---|---|---|
| Age, years (mean ± SD) | 62 ± 8 | 62 ± 11 | 62 ± 10 | 59 ± 19 | 0.963 |
| Male, n (%) | 10 (62.5) | 23 (88.5) | 6 (100) | 1 (50.0) | 0.077 |
| Female, n (%) | 6 (37.5) | 3 (11.5) | 0 (0) | 1 (50.0) | |
| BMI, kg/m² (mean ± SD) | 23.7 ± 3.4 | 23.1 ± 4.9 | 21.5 ± 1.8 | 20.5 ± 0.9 | 0.583 |
| Current or ex-smoker, n (%) | 9 (56.3) | 22 (84.6) | 5 (83.3) | 1 (50.0) | 0.171 |
| Smoking, pack years | 90 ± 42 | 60 ± 44 | 66 ± 69 | 15 ± 21 | 0.174 |
| Alcohol use, n (%) | 7 (43.8) | 9 (34.6) | 2 (33.3) | 0 (0) | 0.663 |
| mMRC grade ≥ 2, n (%) | 10 (62.5) | 18 (69.2) | 5 (83.3) | 2 (100) | 0.042 |
| ≥ 2 exacerbations in past year, n (%) | 4 (25.0) | 14 (53.8) | 3 (50.0) | 2 (100) | 0.775 |
| Pedal oedema, n (%) | 3 (18.8) | 7 (26.9) | 1 (16.7) | 0 (0) | 0.770 |
| Eosinopenia, n (%) | 2 (12.5) | 9 (34.6) | 4 (66.7) | 1 (50.0) | 0.091 |

SD, standard deviation; BMI, body mass index; mMRC, modified Medical Research Council. p values derived from one-way analysis of variance for continuous variables and chi-square test for categorical variables.

Spirometric indices across GOLD grades are shown in Table 2. Mean percentage predicted FEV1 fell from 81 ± 3% in mild disease to 58 ± 7% in moderate and 42 ± 15% in severe disease, with an overall cohort mean of 63 ± 16% ($p < 0.001$). Mean percentage predicted FVC fell in parallel from 118 ± 5% to 93 ± 10% and 75 ± 17%, with an overall mean of 99 ± 17% ($p < 0.001$). The FEV1/FVC ratio decreased from 0.68 ± 0.01 in mild disease through 0.62 ± 0.04 and 0.53 ± 0.07 to 0.25 ± 0.04 in very severe disease, with an overall mean of 0.61 ± 0.10 ($p < 0.001$). The two patients classified as very severe had a mean percentage predicted FEV1 of 44 ± 34%, reflecting the wide dispersion produced by an extremely small subgroup.

Table 2: Pulmonary function test parameters by GOLD grade of airflow limitation (n = 50)

| Parameter | Mild (n=16) | Moderate (n=26) | Severe (n=6) | Very severe (n=2) | Total (n=50) | p value |
|---|---|---|---|---|---|---|
| FEV1, % predicted | 81 ± 3 | 58 ± 7 | 42 ± 15 | 44 ± 34 | 63 ± 16 | <0.001 |
| FVC, % predicted | 118 ± 5 | 93 ± 10 | 75 ± 17 | 101 ± 18 | 99 ± 17 | <0.001 |
| FEV1/FVC ratio | 0.68 ± 0.01 | 0.62 ± 0.04 | 0.53 ± 0.07 | 0.25 ± 0.04 | 0.61 ± 0.10 | <0.001 |

Values expressed as mean ± standard deviation. FEV1, forced expiratory volume in one second; FVC, forced vital capacity. p values derived from one-way analysis of variance.

Carotid intima-media thickness increased in a stepwise fashion with worsening airflow limitation, as shown in Table 3. Mean CIMT was 0.90 ± 0.16 mm in mild disease, 1.13 ± 0.26 mm in moderate disease, 1.60 ±

0.14 mm in severe disease and 1.95 ± 0.07 mm in very severe disease, with a pooled cohort mean of 1.15 ± 0.34 mm; the difference across grades was highly significant ($p < 0.001$). The absolute increment between mild and severe disease was 0.70 mm, representing a relative increase of approximately 78%. Mean CIMT exceeded the conventional abnormality threshold of 1.0 mm in every group except the mild group, and exceeded the plaque threshold of 1.5 mm in the severe and very severe groups.

Table 3: Carotid intima-media thickness by GOLD grade of airflow limitation (n = 50)

| GOLD grade | n (%) | Mean CIMT (mm) | SD | Increment over mild | p value |
|---|---|---|---|---|---|
| Mild | 16 (32.0) | 0.90 | 0.16 | Reference | <0.001 |
| Moderate | 26 (52.0) | 1.13 | 0.26 | +0.23 mm | |
| Severe | 6 (12.0) | 1.60 | 0.14 | +0.70 mm | |
| Very severe | 2 (4.0) | 1.95 | 0.07 | +1.05 mm | |
| Total | 50 (100) | 1.15 | 0.34 | | |

CIMT, carotid intima-media thickness; SD, standard deviation. p value derived from one-way analysis of variance across the four GOLD grades.

Laboratory parameters stratified by GOLD grade are summarised in Table 4. Serum uric acid rose consistently with severity, from 4.3 ± 1.3 mg/dL in mild disease to 5.6 ± 1.1 mg/dL in moderate, 7.7 ± 1.6 mg/dL in severe and 7.1 ± 2.1 mg/dL in very severe disease, with an overall mean of 5.5 ± 1.7 mg/dL ($p < 0.001$). Haemoglobin also differed significantly across grades at 14.5 ± 2.4, 15.7 ± 1.3, 16.0 ± 1.0 and 12.9 ± 2.7 g/dL respectively ($p = 0.036$), the higher values in moderate and severe disease being consistent with secondary polycythaemia and the lower value in the very severe group reflecting only two patients. Total leucocyte count, platelet count, random blood sugar, blood urea, serum creatinine, bilirubin, total protein, albumin, prothrombin time, international normalised ratio, serum sodium and serum potassium did not differ significantly across grades (all $p > 0.05$). Notably, mean blood urea in the very severe group was 41.8 ± 10.3 mg/dL compared with 25.2 to 26.5 mg/dL in the other groups, but this did not reach significance ($p = 0.125$). Eosinopenia was present in 16 patients (32%) overall and its frequency rose from 12.5% in mild to 66.7% in severe disease without reaching significance ($p = 0.091$).

Table 4: Laboratory parameters by GOLD grade of airflow limitation (n = 50)

| Parameter | Mild (n=16) | Moderate (n=26) | Severe (n=6) | Very severe (n=2) | Total (n=50) | p value |
|---|---|---|---|---|---|---|
| Haemoglobin, g/dL | 14.5 ± 2.4 | 15.7 ± 1.3 | 16.0 ± 1.0 | 12.9 ± 2.7 | 15.3 ± 1.9 | 0.036 |
| Total leucocyte count, /mm³ | 7095 ± 1398 | 7694 ± 2016 | 7148 ± 2336 | 9675 ± 813 | 7516 ± 1877 | 0.276 |
| Platelet count, lakh/mm³ | 5.17 ± 2.40 | 2.51 ± 0.67 | 2.04 ± 0.58 | 2.88 ± 0.03 | 3.32 ± 1.96 | 0.560 |
| Random blood sugar, mg/dL | 121 ± 25 | 135 ± 35 | 134 ± 28 | 119 ± 13 | 130 ± 31 | 0.470 |
| Serum uric acid, | 4.3 ± 1.3 | 5.6 ± 1.1 | 7.7 ± 1.6 | 7.1 ± 2.1 | 5.5 ± 1.7 | <0.001 |

| | | | | | | |
|---|---|---|---|---|---|---|
| mg/dL | | | | | | |
| Blood urea, mg/dL | 25.5 ± 8.9 | 26.5 ± 8.9 | 25.2 ± 9.5 | 41.8 ± 10.3 | 26.6 ± 9.3 | 0.125 |
| Serum creatinine, mg/dL | 0.71 ± 0.25 | 0.66 ± 0.24 | 0.73 ± 0.25 | 0.70 ± 0.00 | 0.69 ± 0.24 | 0.850 |
| Total protein, g/dL | 6.4 ± 0.6 | 6.5 ± 0.9 | 5.9 ± 1.5 | 5.6 ± 0.2 | 6.4 ± 0.9 | 0.330 |
| Serum albumin, g/dL | 3.3 ± 0.4 | 3.4 ± 0.8 | 3.4 ± 0.7 | 2.9 ± 0.4 | 3.3 ± 0.7 | 0.822 |
| Prothrombin time, s | 10.9 ± 0.9 | 11.4 ± 0.9 | 11.0 ± 0.6 | 9.9 ± 0.4 | 11.1 ± 0.9 | 0.079 |
| INR | 1.04 ± 0.13 | 0.98 ± 0.08 | 0.94 ± 0.04 | 0.98 ± 0.09 | 0.99 ± 0.10 | 0.140 |
| Serum sodium, mEq/L | 138 ± 5 | 138 ± 4 | 136 ± 3 | 137 ± 0 | 138 ± 4 | 0.824 |
| Serum potassium, mEq/L | 3.7 ± 0.6 | 3.8 ± 0.6 | 4.0 ± 0.2 | 4.0 ± 0.0 | 3.8 ± 0.6 | 0.721 |

Values expressed as mean ± standard deviation. INR, international normalised ratio. p values derived from one-way analysis of variance.

Correlation analysis between carotid intima-media thickness and pulmonary function indices is presented in Table 5. CIMT showed a moderate and highly significant inverse correlation with percentage predicted FEV1 (r = -0.557, p < 0.001) and a weaker but still significant inverse correlation with percentage predicted FVC (r = -0.389, p = 0.005). The strongest relationship was with the FEV1/FVC ratio (r = -0.703, p <0.001), indicating that approximately 49% of the variance in carotid wall thickness in this cohort was explained by the degree of airflow obstruction. In contrast, CIMT showed no significant correlation with age (r = -0.095, p = 0.510), which is important because age is ordinarily the single strongest determinant of carotid wall thickness in unselected populations.

Table 5: Pearson correlation of carotid intima-media thickness with age and pulmonary function indices (n = 50)

| Variable correlated with CIMT | Pearson r | p value (2-tailed) | n | Significance |
|---|---|---|---|---|
| Age, years | -0.095 | 0.510 | 50 | Not significant |
| FEV1, % predicted | -0.557 | <0.001 | 50 | Significant |
| FVC, % predicted | -0.389 | 0.005 | 50 | Significant |
| FEV1/FVC ratio | -0.703 | <0.001 | 50 | Significant |

CIMT, carotid intima-media thickness; FEV1, forced expiratory volume in one second; FVC, forced vital capacity.

In-hospital mortality occurred in 14 patients (28%) overall, with a frequency of 25.0% in mild, 23.1% in moderate, 33.3% in severe and 100% in very severe disease; the difference across grades did not reach significance (p = 0.132), most likely reflecting the very small number of patients in the two highest severity grades. Receiver operating characteristic analysis of carotid intima-media thickness for the prediction of in-hospital mortality is summarised in Table 6. The area under the curve was 0.940 with a standard error of 0.039

and a 95% confidence interval of 0.835 to 0.988 (z = 11.304, p < 0.0001). The Youden index was maximised at 0.8016 at a CIMT cut-off above 1.4 mm, which yielded a sensitivity of 85.71% and a specificity of 94.44%.

Table 6: Receiver operating characteristic analysis of carotid intima-media thickness for prediction of in-hospital mortality (n = 50)

| Parameter | Value | Remarks |
|---|---|---|
| Area under the curve | 0.940 | Excellent discrimination |
| Standard error | 0.039 | |
| 95% confidence interval | 0.835 to 0.988 | Lower bound well above 0.5 |
| z statistic | 11.304 | |
| p value (area = 0.5) | <0.0001 | Statistically significant |
| Youden index J | 0.8016 | Maximal at optimal cut-off |
| Optimal cut-off | CIMT > 1.4 mm | |
| Sensitivity | 85.71% | 12 of 14 deaths correctly identified |
| Specificity | 94.44% | 34 of 36 survivors correctly identified |

CIMT, carotid intima-media thickness. Analysis based on 14 in-hospital deaths and 36 survivors.

**Discussion**

This cross-sectional study of 50 patients with spirometry-confirmed COPD, deliberately selected to exclude diabetes mellitus, hypertension, ischaemic heart disease, cerebrovascular disease and treatment with statins or antiplatelet agents, demonstrates that carotid intima-media thickness rises progressively with worsening airflow limitation and correlates inversely and strongly with spirometric indices. The absence of any significant correlation between CIMT and age in this cohort strengthens the inference that the observed carotid thickening is driven by the disease process rather than by chronological ageing.

The magnitude and direction of our findings are consistent with the international literature. Iwamoto and colleagues studied middle-aged men and reported significantly greater mean CIMT in smokers with airflow limitation (0.78 mm) than in control smokers (0.73 mm, p < 0.01) and never smokers (0.73 mm, p < 0.005), together with a markedly higher prevalence of carotid plaque in those with airflow limitation (73.8% versus 48.4%, p < 0.005).[14] Their central conclusion, that atherosclerotic change begins early in the natural history of COPD, is echoed in our data by the observation that mean CIMT had already reached 1.13 mm in patients with only moderate airflow limitation.van Gestel and co-workers, studying 585 patients undergoing vascular surgery, found increased carotid wall thickness defined as 1.25 mm or more in 23% of patients without COPD, 32% of those with mild COPD and 36% of those with moderate to severe COPD (p < 0.01), and identified COPD as an independent determinant of increased wall thickness after adjustment for age and smoking.[15] The graded relationship they described across severity categories is reproduced in our cohort in continuous form.

Population-based cohorts support the same association. In the Atherosclerosis Risk in Communities study,

impaired lung function was associated with subclinical carotid atherosclerosis, and carotid wall thickness independently predicted incident coronary heart disease.[13] Analyses from the MESA Lung Study linked airflow obstruction and radiographic emphysema to subclinical atherosclerosis in a multi-ethnic population free of clinical cardiovascular disease at baseline.[17] In the Rotterdam Study, participants with COPD not only had thicker carotid walls but also a higher frequency of lipid core containing plaque on magnetic resonance imaging, and COPD emerged as an independent predictor of plaque vulnerability rather than merely of plaque quantity.[16] A meta-analysis of literature studies confirmed that both CIMT and the prevalence of carotid plaque are significantly greater in patients with COPD than in comparison groups, with the effect persisting in sensitivity and subgroup analyses.[18] Our correlation coefficients of -0.557 for FEV1 and -0.703 for the FEV1/FVC ratio are at the stronger end of the reported range, which is plausibly a consequence of our restrictive exclusion criteria: by removing patients with diabetes, hypertension and established coronary disease, much of the competing variance in carotid wall thickness was eliminated, allowing the contribution of airflow limitation to emerge more clearly.

Indian data are concordant. Chindhi and colleagues, in a prospective hospital-based case-control study of 142 patients with COPD and 124 controls, reported carotid plaque in 38.7% of patients with COPD compared with 13.7% of controls, and recommended that carotid screening be incorporated into cardiovascular assessment in COPD.[19] Singh and co-workers, studying patients with COPD in the explicit absence of known atherosclerotic risk factors, reported a strong inverse and statistically significant correlation between percentage predicted FEV1 and CIMT, a design closely parallel to ours and a finding our data replicate.[20] Kim and colleagues similarly demonstrated increased carotid atherosclerosis in patients with untreated COPD, again arguing against pharmacological confounding as an explanation.[21]

Not all published work is uniformly concordant, and the discrepancies are instructive. Golpe and co-workers, comparing patients with COPD to control smokers, found that subclinical carotid atherosclerosis was common in both groups and questioned whether the difference attributable to COPD itself is large once smoking is adequately matched.[22] More recently, a cross-sectional study of 106 patients with stable COPD reported significant differences in CIMT across GOLD stages but, in contrast to our findings, identified no direct correlation with FEV1, with the greatest increment in carotid wall thickness occurring in the early stages of disease.[23] Two methodological factors probably explain such divergence. First, most comparator studies enrolled clinically stable outpatients, whereas all our patients were assessed during an exacerbation, a state associated with a surge in inflammatory mediators, hypoxaemia and haemodynamic stress that may amplify measured wall thickness. Second, cohorts that permit diabetes, hypertension and dyslipidaemia introduce competing determinants of CIMT that attenuate the apparent contribution of airflow limitation. Our restrictive design reduces confounding but at the price of generalisability, since the typical patient with COPD encountered in routine practice frequently carries precisely these comorbidities.

The prognostic dimension of our findings deserves comment. Köseoğlu and colleagues showed that CIMT above 1.25 mm identified patients with COPD who had

a twelve-fold increased risk of angiographically significant coronary artery disease.[24] van Gestel and co-workers reported higher total and cardiovascular mortality among patients with COPD and increased carotid wall thickness, and Gulbas and colleagues, in a multicentre prospective study, confirmed that CIMT carries prognostic information for survival in COPD.[15,25]

In our cohort, CIMT discriminated in-hospital mortality with an area under the curve of 0.940 and an optimal cut-off above 1.4 mm giving 85.71% sensitivity and 94.44% specificity. This figure should be interpreted with considerable caution. The analysis rests on only 14 events, the cut-off was derived and tested in the same small dataset without internal or external validation, and CIMT is correlated with severity of airflow limitation, which is itself the dominant determinant of short-term mortality in an exacerbation.

The observed discrimination therefore reflects, at least in part, the association between carotid thickening and disease severity rather than an independent causal contribution of the carotid wall to short-term survival. The finding is best regarded as hypothesis generating and requires confirmation in an adequately powered prospective cohort with multivariable adjustment.

Two ancillary laboratory observations merit brief discussion. Serum uric acid increased significantly with severity of airflow limitation, from 4.3 mg/dL in mild disease to 7.7 mg/dL in severe disease ($p < 0.001$). Hyperuricaemia in COPD is attributed to tissue hypoxia with accelerated adenosine triphosphate degradation and purine turnover, and elevated uric acid has itself been associated with endothelial dysfunction and adverse cardiovascular outcomes, offering a plausible metabolic link between hypoxaemia and vascular injury. Haemoglobin also varied significantly across grades ($p = 0.036$), with higher values in moderate and severe disease consistent with secondary erythrocytosis due to chronic hypoxaemia. Increased haematocrit raises blood viscosity and shear stress and has been implicated in the progression of arterial wall thickening, providing a further mechanistic thread connecting the severity of airflow limitation to carotid remodelling.

Taken together with existing evidence, our findings support a model in which COPD and atherosclerosis share a common inflammatory and oxidative substrate rather than merely co-occurring by virtue of shared exposure to tobacco.[8,9] Systemic spillover of pulmonary inflammation, sustained and intermittent hypoxaemia, oxidative stress, endothelial dysfunction and the prothrombotic milieu of repeated exacerbations plausibly act in concert on the arterial wall, and the degree of airflow limitation serves as an accessible clinical index of the cumulative intensity of that process. The practical implication is that spirometry, which is widely available and inexpensive, can be used to flag those patients with COPD in whom carotid imaging and intensive cardiovascular risk reduction are most likely to be worthwhile. Where carotid Doppler ultrasonography is unavailable, as is common in peripheral health facilities in India, the severity of airflow limitation alone should prompt aggressive smoking cessation support, pulmonary rehabilitation, vaccination, treatment of hypoxaemia and attention to modifiable vascular risk, since these patients carry a substantial and largely unrecognised burden of subclinical atherosclerosis.

**Limitations**

This study has several limitations. The sample size of 50 was modest and the severe and very severe groups contained only six and two patients respectively, which limits the precision of estimates in those strata and

probably explains the failure of several plausible gradients, including body mass index and mortality, to reach statistical significance. There was no control group of individuals with normal lung function, so the absolute contribution of COPD to carotid wall thickness relative to the background population cannot be quantified from these data. The cross-sectional design precludes any inference about causality or about the temporal sequence of airflow limitation and carotid thickening. All patients were recruited during an exacerbation, which may have inflated measured carotid wall thickness and limits comparability with studies of stable outpatients. Carotid intima-media thickness is operator dependent, and although all studies were performed by a single experienced radiologist, no formal assessment of intra-observer or inter-observer reproducibility was undertaken. Inflammatory markers such as C-reactive protein and fibrinogen, lipid profile and arterial blood gas indices were not analysed as covariates, so the proposed inflammatory and hypoxaemic mechanisms could not be tested directly. Finally, the deliberate exclusion of patients with diabetes, hypertension, coronary disease and vasoactive drug therapy, while methodologically desirable, restricts generalisability to the broader COPD population in whom these comorbidities are common. Multicentric and community-based studies with a longer duration of follow-up, a matched control group and adjustment for inflammatory biomarkers are required to confirm and extend these observations.

**Conclusion**

In this hospital-based cross-sectional study of 50 patients with spirometry-confirmed COPD and no conventional atherosclerotic risk factors, carotid intima-media thickness increased in a graded fashion with worsening airflow limitation, from a mean of 0.90 mm in mild disease to 1.13 mm in moderate, 1.60 mm in severe and 1.95 mm in very severe disease ($p < 0.001$). Carotid wall thickness correlated inversely and significantly with percentage predicted FEV1 ($r = -0.557$, $p < 0.001$), percentage predicted FVC ($r = -0.389$, $p = 0.005$) and the FEV1/FVC ratio ($r = -0.703$, $p < 0.001$), while showing no relationship with age. Serum uric acid and haemoglobin also varied significantly with severity, consistent with a hypoxaemic and inflammatory pathway linking the lung to the arterial wall.

These findings indicate that subclinical atherosclerosis is present early in COPD and progresses in parallel with the severity of airflow obstruction, independent of the classical vascular risk factors that were excluded by design. Pulmonary function testing therefore offers more than a respiratory diagnosis: the degree of airflow limitation provides a readily available index of cardiovascular risk. Carotid ultrasonography is a simple, safe and inexpensive investigation that deserves consideration as part of the routine cardiovascular assessment of patients with COPD, particularly those with moderate or worse airflow limitation. The observation that carotid intima-media thickness above 1.4 mm discriminated in-hospital mortality with high sensitivity and specificity is promising but preliminary, and warrants prospective validation in larger cohorts before it can be recommended for clinical use.

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