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Predictors of Impaired Diffusing Capacity of Lung for Carbon Monoxide in Post-COVID-19 Pulmonary Fibrosis Patients

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ABSTRACT

Background & objective: While Acute Respiratory Distress Syndrome (ARDS) is a hallmark of severe COVID-19, survivors often face long-term sequelae, most notably post-COVID-19 Pulmonary Fibrosis (PCPF). The Diffusing Capacity of the Lung for Carbon Monoxide (DLCO) is a sensitive physiological marker for alveolar-capillary integrity. This study aimed to determine the prevalence and predictors of impaired DLCO among patients with radiologically confirmed PCPF in Bangladesh.

Methods: This cross-sectional analytical study was conducted at the Diffuse Parenchymal Lung Disease (DPLD) Clinic, Dhaka Medical College Hospital, from September 2021 to August 2022. Forty-eight patients with PCPF were enrolled. Pulmonary Function Tests (PFTs), including spirometry and DLCO (single-breath technique), were performed at least 12 weeks after acute infection. Patients were categorized into Cases (impaired DLCO < 75% predicted) and Controls (normal DLCO ≥ 75%). Statistical analysis was performed using SPSS, with level of significance set at $p < 0.05$.

Results: The prevalence of impaired DLCO was 27.1% (n=13) in the study cohort. Patients with impaired DLCO were significantly older (62.5 ± 3.4 vs. 53.6 ± 7.9 years; $p < 0.001$) and more likely to be female (61.5% vs. 28.6%; $p = 0.040$). A history of chronic obstructive pulmonary disease (COPD) was a strong predictor of impairment (OR = 9.6; 95% CI: 2.2–41.5; $p = 0.004$). Biochemical markers, including serum creatinine ($p = 0.003$), D-dimer ($p < 0.01$), and C-Reactive protein ($p = 0.008$), were significantly elevated in the impaired group. Furthermore, patients with a history of severe acute COVID-19 illness were 13.5 times more likely to exhibit diminished DLCO (95% CI: 2.9–61.2; $p = 0.001$).

Conclusion: Diminished diffusing capacity of the lung for carbon monoxide is prevalent among PCPF survivors and is strongly associated with advanced age, female gender, pre-existing COPD, and the severity of the initial infection. These findings underscore the importance of routine DLCO monitoring in the post-COVID-19 clinical pathway to facilitate early intervention and improve long-term respiratory outcomes.

Keywords: COVID-19, Pulmonary Fibrosis, Diffusing Capacity of the Lung for Carbon Monoxide (DLCO), Pulmonary Function Test etc.

ORIGINAL ARTICLE

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INTRODUCTION:

The Coronavirus disease 2019 (COVID-19), caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), is a major global health crisis[1]. While the clinical spectrum is wide, a significant number of patients develop severe or critical illness requiring hospitalization[2,3]. Severe COVID-19 pneumonia frequently involves extensive pulmonary damage, predisposing a subset of survivors to long-term sequelae[4].

Pulmonary fibrosis (PF) is a pathological consequence of dysregulated wound-healing following severe lung injury[5]. The SARS-CoV-2 virus targets the lungs by utilizing the angiotensin-converting enzyme 2 (ACE2) receptor on Type II alveolar cells[6]. Both direct viral damage and immune-mediated responses contribute to lung scarring (fibrosis)[7]. Consequently, a substantial cohort of post-COVID-19 patients develops restrictive lung disease and PF, often presenting with persistent respiratory symptoms[7,8]. Observational data suggests that pulmonary sequelae, including fibrosis, are prevalent three months post-recovery[9].

Post-COVID-19 Pulmonary Fibrosis (PCPF) is defined by persistent fibrotic changes on follow-up computed tomography (CT) scans, which frequently correlate with functional respiratory impairment. The pathogenesis involves a progression from acute respiratory distress syndrome (ARDS) to fibrosis, marked by diffuse alveolar damage (DAD), dysregulated inflammation, and unchecked fibroproliferation, leading to thickening of the alveolar-capillary membrane[10]. Vascular dysfunction and microthrombi are also implicated, contributing to compromised gas exchange[11]. Risk factors for PCPF include advanced age, male gender, comorbidities, and acute phase characteristics like prolonged hospitalization, mechanical ventilation, and elevated inflammatory markers[12]. Among the observed pulmonary function abnormalities in post-COVID-19 patients, impairment of the Diffusing Capacity of the Lung for Carbon Monoxide (DLCO) is the most common finding[13]. DLCO is a crucial measurement quantifying the lung's efficiency in transferring gas into the bloodstream[14]. Its reduction in interstitial lung diseases, like PF, is primarily due to the thickening of the alveolar-capillary membrane and potential microvascular damage[11,15].

Guidelines recommend Pulmonary Function Tests (PFTs), including DLCO, for monitoring PF progression[16]. International studies consistently report a high prevalence of impaired diffusion capacity in post-COVID-19 patients[17,18]. Given the limited specific data in Bangladesh regarding DLCO alteration and its correlation with PCPF, this study is critically important.

METHODS:

This cross-sectional analytical study was conducted over one year, from September 2021 to August 2022, at the Diffuse Parenchymal Lung Disease (DPLD) Clinic within the Department of Respiratory Medicine at Dhaka Medical College & Hospital (DMCH), Dhaka, Bangladesh. The study included a sample of 48 patients diagnosed with post-COVID-19 Pulmonary Fibrosis (PCPF). Eligibility required patients to be 18 years or older, presenting at least twelve weeks after acute COVID-19 onset, and providing informed consent. However, patients with known DPLD, active infections (like pulmonary tuberculosis), or a history of receiving drugs (e.g., bleomycin, methotrexate, amiodarone, nitrofurantoin) or radiation known to induce pulmonary fibrosis were excluded. Patients were later classified into Cases (PCPF with impaired DLCO) and Controls (PCPF with normal DLCO).

Data collection involved gathering relevant socio-demographic data (age, sex, and body mass index or BMI) and pertinent medical history via a semi-structured questionnaire, interviews, and hospital record review. A thorough clinical examination included recording vital signs (pulse rate, respiratory rate, and blood pressure) and measuring Oxygen Saturation (SpO^2) using a digital pulse oximeter. Furthermore, the presence and severity of pulmonary fibrosis were objectively confirmed and assessed using High-Resolution Computed Tomography (HRCT) scans of the chest evaluated by a specialist physician.

All patients underwent Pulmonary Function Testing (PFT), specifically spirometry and the DLCO, following American Thoracic Society (ATS) guidelines. The DLCO was measured using the standardized single-breath technique. This procedure involved the patient exhaling fully, rapidly inhaling the test gas to Total Lung Capacity (TLC), maintaining a breath-hold for 10 seconds, and then exhaling forcefully for alveolar gas sampling and analysis. The final DLCO value, calculated from the gas concentrations, lung volume, and breath-holding time, was based on an average of two or more satisfactory attempts. The DLCO value of < 75% of the predicted value was termed impaired (Case) and that of ≥ 75% as normal (Control).

Data processing and analysis were conducted using SPSS (Statistical Package for Social Sciences) software. Categorical data were compared between Case and Control groups using the Chi-square (χ^2) Test, and continuous data were compared between groups using the Unpaired t-Test. Furthermore, the Odds Ratio (OR) with its 95% Confidence Interval (CI) was calculated to estimate the risk of developing impaired DLCO. The level of statistical significance was set at 5% and a p-value < 0.05 was considered significant.

RESULTS:

Prevalence and Demographic Characteristics

Of the 48 patients diagnosed with post-COVID-19 Pulmonary Fibrosis (PCPF), 13(27.1%) exhibited impaired diffusing capacity (DLCO < 75% of predicted), while 35(72.9%) maintained normal DLCO levels.

Comparative analysis of demographic variables (Table I) revealed that patients in the Case group were significantly older, with a mean age of 62.5±3.4 years compared to 53.6 ± 7.9 years in the Control group (p < 0.001). Furthermore, a majority of patients with impaired DLCO were aged 60 years or older (69.2%). Gender also emerged as a significant factor, with females constituting a notably higher proportion of the Case group (61.5%) relative to the Control group (28.6%, p=0.040). Conversely, Body Mass Index (BMI), smoking status, and history of alcohol consumption did not demonstrate statistically significant associations with DLCO impairment (p > 0.05).

Clinical Profile and Comorbidities

The relationship between clinical variables and functional impairment is summarized in Table II. A history of Chronic Obstructive Pulmonary Disease (COPD) was strongly associated with diminished diffusing capacity; 61.5% of the Case group had pre-existing COPD compared to only 14.3% of the Control group (p = 0.004). Patients with PCPF and a history of COPD were over nine times more likely to present with impaired DLCO (OR = 9.6; 95% CI: 2.2-41.5). Other comorbidities, including hypertension (HTN), diabetes mellitus (DM), and chronic kidney disease (CKD), did not show significant associations. Regarding symptomatology, persistent cough and fever were significantly more prevalent in the Case group (p = 0.013 and p<0.001, respectively). However, subjective reports of shortness of breath and chest tightness did not differ significantly between the two groups (p=0.927).

Biochemical Parameters

Laboratory findings (Table III) highlighted significant elevations in three key biomarkers among patients with impaired DLCO. Serum Creatinine was observed to be significantly higher in the Case group (1.17 ± 0.45 mg/dl vs. Controls 0.90 ± 0.14 mg/dl; p = 0.003). Mean D-dimer levels were notably elevated in Cases (0.38 ± 0.07 mg/L) compared to Controls (0.29 ± 0.05 mg/L; p<0.01). Cases exhibited significantly higher inflammatory activity, as evidenced by elevated C-Reactive Protein (90 ± 16.3 mg/L) than did their Control counterparts (70 ± 23.8 mg/L; p = 0.008). Hemoglobin levels, white blood cell (WBC) counts, & platelet count remained statistically comparable between groups.

Acute Illness Severity and Hospitalization

The severity of the initial COVID-19 insult was a potent predictor of long-term pulmonary dysfunction (p = 0.001). Patients with a history of severe acute illness were 13.5 times more likely to

develop impaired DLCO (95% CI: 2.9-61.2). Notably, 69.2% of the Case group had survived severe COVID-19, whereas no patients with a history of mild illness progressed to DLCO impairment (Table IV). Interestingly, the total duration of hospital stay during the acute phase did not significantly differ between those who eventually developed impaired DLCO and those who did not (11.5 ± 1.8 days vs. 11 ± 1.4 days; p=0.307)

Table I: Association of demographic and behavioural characteristics with DLCO

Socio-demographic Characteristics	Group		Odds Ratio (95% CI of OR)	p-value
	Case (n = 13)	Control (n = 35)		
Age group (years)				
< 60	4(30.8)	26(74.3)		
≥ 60	9(69.2)	9(25.7)		
Mean ± SD	62.5 ± 3.4	53.6 ± 7.9	Not applicable	< 0.001#
Gender				
Female	8(61.5)	10(28.6)	4.0(1.1 – 15.2)	0.040*
Male	5(38.5)	25(71.4)		
BMI (kg/m2)				
≥ 25 (Overweight/Obese)	4(30.8)	15(42.9)	0.6(0.1 – 2.3)	0.447*
< 25 (Normal)	9(69.2)	20(57.1)		
Smoking habit	4(30.8)	10(28.6)	1.1(0.3 – 4.4)	0.998**
Alcohol habit	3(23.1)	5(14.3)	1.8(0.4 – 8.9)	0.771**

Figures in the parentheses indicate corresponding %; ***Chi-squared Test** (χ^2) was done to analyze the data. #Data were analyze using **Unpaired t-Test** and were presented as **mean ± SD**. ****Fisher's Exact Test** was done to analyze the data.

Table II: Association of clinical characteristics with DLCO

Clinical Characteristics	Group		Odds Ratio (95% CI of OR)	p-value
	Case (n = 13)	Control (n = 35)		
Comorbidities				
HTN	7(53.8)	11(31.4)	2.5(0.7 – 9.3)	0.138*
DM	4(30.8)	10(28.6)	1.1(0.3 – 4.4)	0.573*
COPD	8(61.5)	5(14.3)	9.6(2.2 – 41.5)	0.004*
CKD	1(7.7)	5(14.3)	0.50(0.05 – 4.73)	0.476**
Clinical Presentation				
Cough	13(100.0)	20(57.1)	Not computable	0.013*
Fever	13(100.0)	15(42.9)	Not computable	< 0.001*
Shortness of breath	5(38.5)	10(40.0)	0.9(0.2 – 3.7)	0.927*
Chest tightness	5(38.5)	10(40.0)	0.9(0.2 – 3.7)	0.927*

Figures in the parentheses indicate corresponding %; * ***Chi-squared Test** (χ^2) was done to analyze the data. ****Fisher's Exact Test** was done to analyze the data.

Table III: Association of pertinent biochemical parameters with DLCO

Investigation Findings	Group		p-value
	Case (n = 13)	Control (n = 35)	
Hb (%)	12.6 ± 1.3	13.1 ± 0.7	0.088
WBC (/cu-mm)	6115 ± 650	6571 ± 1030	0.144
Platelet count (/cu-mm)	179231 ± 12558	171429 ± 16653	0.133
Serum creatinine (mg/dl)	1.17 ± 0.45	0.90 ± 0.14	0.003
D-dimer (mg/L)	0.38 ± 0.07	0.29 ± 0.05	< 0.001
CRP (mg/L)	90.0 ± 16.3	70.0 ± 23.8	0.008

#Data were analyze using **Unpaired t-Test** and were presented as **mean ± SD.**

Table IV: Association between severity of disease and DLCO

Severity of Disease	Group		Odds Ratio (95% CI of OR)	p-value
	Case (n = 13)	Control (n = 35)		
Severe	9(69.2)	5(14.3)	13.5(2.9 – 61.2)	0.001*
Mild to Moderate	4(30.8)	30(85.7)		

Figures in the parentheses indicate corresponding %; ***Chi-squared Test** (χ^2) was done to analyze the data.

Table V: Association between duration of hospital stay and DLCO

Duration of hospital stay (days)	Group		p-value
	Case (n = 13)	Control (n = 35)	
≤10	5(38.5)	15(42.9)	
>10	8(61.5)	20(57.1)	
Mean ± SD	11.5 ± 1.8	11.0 ± 1.4	0.307#

Figures in the parentheses indicate corresponding %; # Data were analyze using **Unpaired t-Test** and were presented as **mean ± SD**.

DISCUSSION:

The COVID-19 coronavirus, also known as SARS-CoV-2, spread quickly and is known to cause atypical pneumonia that can escalate to acute lung damage. COVID-19 leads to a wide spectrum of respiratory diseases with an extremely high incidence of acute respiratory distress syndrome. Pulmonary fibrosis is a progressive disease in which lung function inexorably declines, leading to respiratory failure[19]. Pulmonary functional alterations are frequently detected, in particular a reduction in lung diffusion capacity[20]. After leaving the hospital, people with severe COVID-19 display

several ongoing symptoms. About 80% of patients with post-COVID problems had spirometry and DLCO changes, which may indicate functional impairment from lung damage[3].

The current study found that 27.1% had decreased DLCO among those with post-COVID-19 pulmonary fibrosis. Fortini et al. found that 37% of the patients had decreased diffusing lung capacity 3–6 months after discharge[21]. In a previous study, impaired lung function was found in 52% of the subjects, with reduced DLCO as the main finding[22]. Reduced DLCO in pulmonary fibrosis is due to the thickening of the alveolar-capillary membrane[23].

In this study, older age and female gender were significantly associated with impaired DLCO levels. A previous study also revealed that the risk of impaired DLCO increased with age above 60 years[22]. Another study unveiled that the risk of impaired DLCO in female patients recovered from COVID-19 is higher than in their male counterparts, with older age being a major risk factor[24]. Zhao et al. also observed that older cohorts and females are at increased risk for decreasing DLCO25. Maximum fibrotic changes were found in patients ranging from 60 to 88 years[26].

The clinical profile of the study cohort highlights critical predictors of functional impairment. In this study, hypertension was identified as the most prevalent comorbidity, followed by Diabetes Mellitus (DM) and COPD. While hypertension and diabetes were common across the entire cohort, COPD stood out as a statistically significant predictor for impaired DLCO aligning with research by Ekbom et al[22], who noted that pre-existing airway disease significantly limits the lung's ability to recover gas exchange efficiency post-infection. Interestingly, while Zhao et al[25] also found hypertension and diabetes to be the most frequent comorbidities in their Chinese cohort, they suggested that these metabolic conditions contribute more to acute-phase mortality than to long-term fibrotic changes, whereas our data suggests a more direct link between underlying lung health (COPD) and subsequent PCPF severity. Regarding symptomatology, the invariable presence of persistent cough and fever in the impaired group mirrors findings by Polese et al. and Fortini et al., who argued that ongoing symptoms at 12 weeks are indicative of "prolonged COVID-19 sufferings" and active pulmonary remodeling[3,21]. While some studies, such as Balachandar et al. emphasize gastrointestinal issues and headaches in the recovery phase, our study found that respiratory-specific symptoms like cough were more reliable indicators of underlying functional damage as measured by DLCO[26,27].

The biochemical analysis in our study revealed significantly higher levels of serum creatinine, D-dimer, and C-Reactive Protein (CRP) in patients with impaired DLCO. The elevation of D-dimer is particularly noteworthy; it suggests that microvascular injury and persistent endotheliitis pathologies identified by Ackermann et al. play a central role in the thickening of the alveolar-capillary membrane[11]. Our findings are consistent with Zhi et al., who identified D-dimer as a primary risk factor for impaired diffusion[24]. However, while Tanni et al. observed that CRP levels typically normalize shortly after the acute phase, our study observed higher CRP in the impaired group at follow-up, suggesting a state of chronic, low-grade inflammation that may continue to drive fibrotic progression in certain individuals[12].

Finally, the strong association between initial disease severity and DLCO impairment in our study (OR 13.5) reinforces the findings of Mo et al. and Zhi et al.[24,28]. This confirms that the physiological "insult" sustained during the acute phase of severe COVID-19 pneumonia is the primary determinant of long-term restrictive and diffusive defects. By comparing these outcomes to international data, it becomes evident that regardless of geographic location, the biological markers of inflammation and pre-existing respiratory vulnerability are universal predictors of post-COVID pulmonary health.

While this study provides significant insights into the predictors of impaired diffusing capacity in post-COVID-19 pulmonary fibrosis patients within a Bangladeshi context, several limitations must be acknowledged:

Limitations

• **Sample Size and Statistical Constraints:** The study was conducted with a relatively small sample of 48 patients, which precluded multivariate regression analysis, to adjust for confounding variables and identify independent predictors of impaired DLCO.

• **Study Design:** Being a cross-sectional study, it offers only a snapshot of pulmonary function at a specific point in time (at least 12 weeks post-infection), without allow for the assessment of the temporal progression or potential resolution of DLCO impairment over a longer follow-up period.

• **Single-Center Setting:** The research was conducted at a single tertiary care hospital in Dhaka, which limits generalization of the findings to the entire population of Bangladesh.

• **Lack of Baseline Data:** For most patients, pre-COVID-19 pulmonary function test results were unavailable. While patients with known prior diffuse parenchymal lung disease were excluded, it is difficult to definitively determine the extent to which the observed impairments were solely attributable to SARS-CoV-2 infection versus pre-existing, undiagnosed subclinical lung conditions.

• **Potential for Selection Bias:** The study included patients who presented to a specialized DPLD clinic. This may have introduced a selection bias toward symptomatic patients or those with more severe initial presentations, potentially overestimating the prevalence of DLCO impairment compared to the broader population of COVID-19 survivors.

Conclusion:

The findings of this study underscore the significant long-term physiological impact of COVID-19 on respiratory function. Among patients with post-COVID-19 pulmonary fibrosis, nearly one-third exhibited impaired diffusing capacity of the lung for carbon monoxide (DLCO), highlighting a substantial burden of alveolar-capillary membrane dysfunction.

Advanced age, female gender, and pre-existing COPD emerged as primary risk factors for persistent functional impairment. Furthermore, the severity of the initial acute infection and elevated inflammatory and coagulation markers- specifically CRP and D-dimer-were potent predictors of diminished DLCO. Notably, while subjective symptoms such as cough and fever were more prevalent in functionally impaired patients, the duration of hospitalization did not reliably predict long-term pulmonary outcomes.

These results emphasize the critical role of DLCO as a sensitive diagnostic tool in the follow-up of COVID-19 survivors. Incorporating routine pulmonary function testing into post-acute clinical pathways is essential for the early identification of patients at risk for chronic respiratory morbidity. Such a targeted approach will facilitate timely therapeutic interventions & pulmonary rehabilitation, ultimately improving the quality of life for survivors of severe COVID-19 pneumonia in Bangladesh. While this study provides a foundational understanding, further large-scale, multicenter longitudinal research is warranted to assess the long-term reversibility of these fibrotic changes.

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