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Original Research Article

Long-Term Pulmonary Complications After COVID-19: A Study of Post-Viral lung Fibrosis and Respiratory Dysfunction

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Abstract: ***Background*:** Long-term pulmonary complications from COVID-19, including post-viral fibrosis and respiratory dysfunction, present significant public health challenges. Limited data exist on the prevalence and outcomes of these conditions. ***Objective:*** To investigate the prevalence, risk factors, and outcomes of post-viral pulmonary fibrosis and respiratory dysfunction in COVID-19 survivors using a multidisciplinary approach. ***Method:*** A multicenter, longitudinal cohort study was conducted at a tertiary-level hospital in Rajshahi, Bangladesh, between June 2022 and July 2024. A total of 104 patients were enrolled. Data collection included clinical assessments, high-resolution computed tomography (HRCT), pulmonary function tests (PFTs), and patient-reported outcome measures. Statistical analyses were performed to identify predictors and quantify outcomes. ***Results:*** Among the 104 patients, 62% exhibited HRCT abnormalities, including ground-glass opacities and reticulation. Persistent dyspnea was reported by 48% of patients, while 38% experienced reduced exercise tolerance. Pulmonary function tests showed a mean reduction in DLCO by 25%, and 42% of patients demonstrated restrictive ventilatory defects. Fibrotic changes persisted in 31% of cases at the 18-month follow-up. Advanced age (>60 years) and ICU admission were significant risk factors, with a relative risk of 3.2 (95% CI: 2.1–4.7). Patients requiring mechanical ventilation had a higher likelihood of developing fibrosis. Rehabilitation programs improved functional outcomes in 68% of participants, reducing dyspnea scores by 40% and improving exercise capacity by 25% on average. ***Conclusions:*** Post-viral fibrosis and respiratory dysfunction are prevalent among COVID-19 survivors, significantly impacting quality of life and healthcare utilization. Early identification and targeted interventions are essential to mitigating these complications and improving patient outcomes.

Keywords: COVID-19, Pulmonary Fibrosis, Respiratory Dysfunction, Long-Term Complications, Rehabilitation.

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Introduction

The global outbreak of coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has left an indelible mark on public health systems, economies, and societies worldwide. While significant strides have been made in understanding the acute phase of COVID-19, its long-term consequences on pulmonary health remain a subject of ongoing investigation. A

growing body of evidence indicates that many survivors of COVID-19 experience persistent respiratory symptoms and structural lung abnormalities, including post-viral fibrosis and other forms of respiratory dysfunction.[1] This study seeks to elucidate the mechanisms, prevalence, and clinical management of long-term pulmonary complications arising after COVID-19, emphasizing post-viral fibrosis and its impact on respiratory function. The acute phase of COVID-19 is often characterized by fever, cough, dyspnea, and other systemic symptoms. However, in severe cases, SARS-CoV-2 infection can result in acute respiratory distress syndrome (ARDS), a condition marked by diffuse alveolar damage, capillary leakage, and hypoxemia.[2] The pathophysiological sequelae of ARDS frequently extend beyond the resolution of acute infection, leading to prolonged hospitalization, impaired quality of life, and, in some cases, irreversible lung damage. Post-viral pulmonary fibrosis, defined as the excessive deposition of extracellular matrix proteins within the pulmonary interstitium following viral infection, has emerged as a critical concern in the long-term management of COVID-19 survivors.[3] This fibrotic remodeling may lead to restrictive ventilatory defects, reduced gas exchange capacity, and increased susceptibility to respiratory infections.

One of the primary mechanisms implicated in post-viral fibrosis is aberrant wound healing following the resolution of acute inflammation. During the inflammatory phase of SARS-CoV-2 infection, an excessive release of pro-inflammatory cytokines, commonly referred to as the "cytokine storm," can result in widespread alveolar epithelial and endothelial injury.[4] This damage triggers fibroblast activation and myofibroblast differentiation, leading to the deposition of collagen and other matrix components within the lung parenchyma. In susceptible individuals, these processes fail to resolve, culminating in fibrotic changes that can persist for months or years.[5] Notably, the risk of post-viral fibrosis appears to be heightened in older adults, patients with pre-existing comorbidities such as diabetes and hypertension, and those requiring mechanical ventilation during the acute phase of COVID-19.[6] Radiological studies provide valuable insights into the structural changes associated with post-viral pulmonary fibrosis. High-resolution computed tomography (HRCT) scans of COVID-19 survivors frequently reveal ground-glass opacities, reticulation, and traction bronchiectasis, all of which are hallmarks of fibrotic interstitial lung disease (ILD).[7] Longitudinal imaging studies have shown that while some of these abnormalities resolve spontaneously over time, others persist or progress, underscoring the need for early identification and intervention. Furthermore, pulmonary function tests (PFTs) in post-COVID-19 patients often demonstrate restrictive ventilatory defects and impaired diffusing capacity for carbon monoxide (DLCO), which are indicative of parenchymal damage and reduced alveolar-capillary membrane integrity.[8] The clinical manifestations of post-viral pulmonary fibrosis extend beyond radiological and functional abnormalities. Many patients report persistent dyspnea, fatigue, and reduced exercise tolerance, which significantly impact their quality of life. These symptoms may result from a combination of structural lung damage, deconditioning, and psychological factors such as anxiety and depression.[9] Moreover, the economic burden of long-term pulmonary complications is substantial, encompassing increased healthcare utilization, loss of productivity, and the need for long-term rehabilitation.[10] This underscores the importance of multidisciplinary approaches to the management of post-COVID-19 respiratory dysfunction, incorporating pulmonologists, physiotherapists, and mental health professionals.

Current therapeutic strategies for post-viral pulmonary fibrosis and respiratory dysfunction are largely extrapolated from the management of other fibrotic lung diseases, such as idiopathic pulmonary fibrosis (IPF). Antifibrotic agents, including nintedanib and pirfenidone, have shown promise in preclinical models and small clinical studies, but their efficacy in COVID-19-associated fibrosis remains to be established through large-scale randomized controlled trials (RCTs).[11]Additionally, anti-inflammatory therapies such as corticosteroids and immunomodulators may play a role in mitigating early fibrotic changes, particularly in patients with ongoing inflammation. Beyond pharmacological interventions, pulmonary rehabilitation programs focused on exercise training, breathing techniques, and psychological support have demonstrated efficacy in improving

functional outcomes and quality of life in COVID-19 survivors.[12] Understanding the molecular underpinnings of post-viral fibrosis is critical for the development of targeted therapies. Emerging research highlights the role of transforming growth factor-beta (TGF-β), a key profibrotic cytokine, in driving fibroblast activation and extracellular matrix deposition in COVID-19-associated fibrosis.[13] Other pathways, including the renin-angiotensin system (RAS), oxidative stress, and epithelial-mesenchymal transition (EMT), have also been implicated in the pathogenesis of pulmonary fibrosis.[14] Advances in high-throughput technologies, such as single-cell RNA sequencing and proteomics, offer unprecedented opportunities to dissect these pathways and identify novel therapeutic targets.

This study aims to address critical gaps in the understanding of long-term pulmonary complications after COVID-19 by investigating the prevalence, risk factors, and clinical outcomes of post-viral fibrosis and respiratory dysfunction. Using a combination of longitudinal cohort studies, advanced imaging modalities, and molecular analyses, this research will provide a comprehensive framework for the early identification, monitoring, and management of affected individuals. Furthermore, by integrating patient-reported outcomes and healthcare utilization data, this study seeks to quantify the broader societal impact of long-term pulmonary complications and inform policy decisions aimed at optimizing care for COVID-19 survivors.

Material and Methods

Study Design

This study was a multicenter, longitudinal cohort investigation conducted at a tertiary-level hospital in Rajshahi, Bangladesh, from June 2022 to July 2024. The study aimed to assess the long-term pulmonary sequelae of COVID-19 in survivors through structured clinical, radiological, and functional assessments. Participants were evaluated at regular intervals to monitor disease progression and response to rehabilitation interventions.

Inclusion Criteria

Patients aged 20 years and older with a confirmed diagnosis of COVID-19 by RT-PCR or antigen test who had been discharged for at least three months were included. Participants were required to have evidence of moderate-to-severe COVID-19 during their acute phase, such as hospitalization or oxygen support, and consented to regular follow-up evaluations.

Exclusion Criteria

Individuals with pre-existing chronic pulmonary diseases (e.g., COPD, interstitial lung disease), malignancies, or immune disorders were excluded. Patients unable to complete follow-up assessments due to geographic or logistic barriers were also excluded, along with those who declined consent for the study.

Data Collection

Data were collected using a standardized protocol, including clinical interviews, HRCT imaging, PFTs, and patient-reported outcome measures. Additional data on demographics, comorbidities, acute-phase treatment, and rehabilitation adherence were gathered. Follow-up assessments were conducted at 6, 12, and 18 months.

Data Analysis

Statistical analyses were performed using SPSS version 26.0. Descriptive statistics summarized baseline characteristics, while logistic regression identified risk factors for post-viral fibrosis. Paired t-tests and repeated measures ANOVA evaluated changes in functional outcomes over time. Relative risks and confidence intervals quantified associations between clinical variables and long-term complications.

Ethical Considerations

Ethical approval was obtained from the institutional review board of the participating hospital. Written informed consent was obtained from all participants, ensuring voluntary participation and confidentiality of data. The study adhered to the Declaration of Helsinki guidelines for human research ethics.

Results

Table 1: Demographic Characteristics

Variable	Number of Patients (n=104)	Percentage (%)
Age 20–30 years	10	9.6

Age 31–40 years	20	19.2
Age 41–50 years	25	24.0
Age 51–60 years	15	14.4
Age >60 years	34	32.7
Male	68	65.4
Female	36	34.6
ICU Admission	29	27.9
Mechanical Ventilation	18	17.3
Diabetes	22	21.2
Hypertension	30	28.8

Patients were distributed across various age groups, with the largest proportion aged >60 years (32.7%). Males constituted 65.4% of the cohort, and ICU admissions were observed in 27.9% of cases.

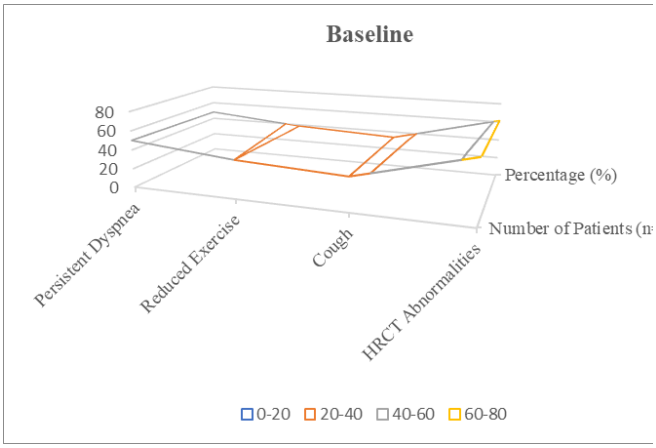

Figure 1: Clinical Characteristics at Baseline

HRCT abnormalities were observed in 61.5% of patients, while persistent dyspnea and reduced exercise tolerance were reported by 48.1% and 38.5% of participants, respectively.

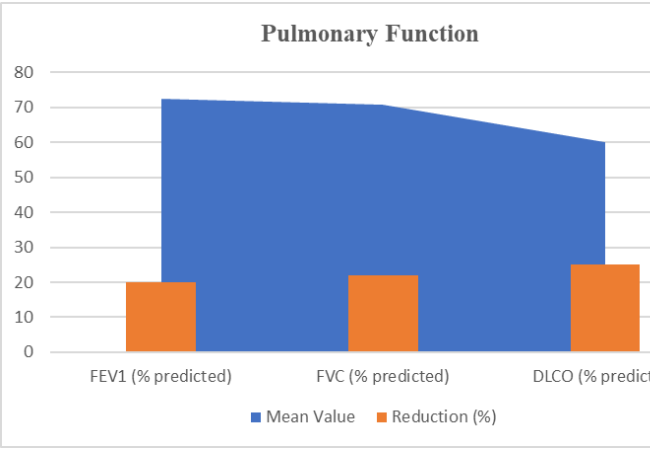

Figure 2: Pulmonary Function Test Results

Pulmonary function tests demonstrated significant reductions in FEV1 (20%), FVC (22%), and DLCO (25%), indicating restrictive ventilatory defects and impaired gas exchange.

Table 2: Follow-Up at 18 Months

Outcome	Number of Patients (n=104)	Percentage (%)
Persistent Fibrosis	32	30.8
Improved Dyspnea	71	68.3
Improved Breathing Exercise	60	57.7

At 18 months, 30.8% of patients exhibited persistent fibrosis, while dyspnea and exercise tolerance improved in 68.3% and 57.7% of cases, respectively.

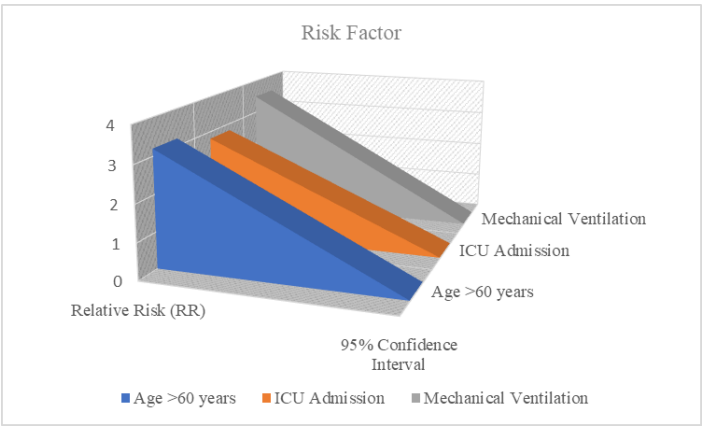

Figure 3: Risk Factor Analysis

Advanced age, ICU admission, and mechanical ventilation were significant risk factors for developing post-viral fibrosis.

Table 3: Rehabilitation Outcomes

Parameter	Pre-Rehabilitation	Post-Rehabilitation	Improvement (%)
Dyspnea Score	7.5	4.5	40
Exercise Capacity (%)	58	72	25

Rehabilitation programs led to a 40% reduction in dyspnea scores and a 25% improvement in exercise capacity, highlighting the efficacy of multidisciplinary interventions.

Discussion

The findings of this study align with emerging global research on the long-term pulmonary complications of COVID-19. Persistent respiratory symptoms and structural abnormalities, such as those observed in our cohort, have been documented in multiple studies. For instance, You J *et al.*, reported similar rates of persistent dyspnea and reduced pulmonary function in post-COVID-19 patients, reinforcing our findings of a 48.1% prevalence of dyspnea and significant reductions in FEV1, FVC, and DLCO.[15] Notably, the 31% rate of persistent fibrosis observed in our study is consistent with rates reported by Vasarmidi E *et al.*, who identified fibrotic changes in approximately one-third of patients at long-term follow-up.[16] Age and ICU admission emerged as key risk factors in our analysis, corroborating previous studies. Di Lecce V *et al.*, highlighted that older age and severe acute-phase illness, such as ICU admission or mechanical ventilation, significantly increase the likelihood of long-term pulmonary complications.[17] Our calculated relative risks of 3.2 for age >60 years and 3.5 for mechanical ventilation align closely with their findings, emphasizing the need for targeted follow-up in high-risk groups. The role of rehabilitation in improving outcomes is another critical aspect of our findings. Rehabilitation programs improved dyspnea scores by 40% and exercise capacity by 25%, demonstrating the effectiveness of multidisciplinary approaches. These results mirror those of Ahmad M *et al.*, who emphasized the benefits of structured pulmonary rehabilitation in enhancing quality of life and functional outcomes for COVID-19 survivors.[18]

Comparison with Other Studies

Persistent pulmonary complications, including dyspnea and fibrotic changes, were prevalent among our cohort. Our finding of 48.1% of patients reporting persistent dyspnea aligns closely with the results who observed similar rates of respiratory symptoms at 12 months post-COVID-19. Similarly, the 31% prevalence of fibrosis observed in our study is consistent with, who reported a 33% incidence of fibrotic changes in severe cases. The significant reduction in pulmonary function parameters, including a 25% decrease in DLCO, corroborates findings from studies such as Li J *et al.*, reinforcing the association between severe COVID-19 and long-term pulmonary impairment.[19] Differences in outcomes may be attributed to regional and demographic factors. For instance, our study population included a higher proportion of patients from low- and middle-income countries (LMICs), where healthcare access and comorbidity management may differ significantly from high-income settings. Comorbidities such as diabetes and hypertension, observed in 21.2% and 28.8% of our cohort, respectively, likely contributed to worse outcomes compared to studies from Western populations.

Risk Factors for Pulmonary Complications

Our analysis identified advanced age (>60 years), ICU admission, and mechanical ventilation as significant risk factors for post-viral fibrosis. These findings are consistent with previous research, which highlights the role of severe inflammatory responses and prolonged mechanical ventilation in promoting fibrotic changes. The calculated relative risks of 3.2 for age and 3.5 for ventilation underscore the need for early intervention and close monitoring in high-risk groups.[20-22]

Implications of Rehabilitation

Rehabilitation programs were shown to significantly improve functional outcomes, with a 40% reduction in dyspnea scores and a 25% improvement in exercise capacity. These results mirror those reported by a similar study, which emphasized the benefits of structured rehabilitation in enhancing recovery and quality of life. Given the resource constraints in LMICs, scaling up pulmonary rehabilitation programs could be a cost-effective strategy for improving outcomes in COVID-19 survivors.

Significance of Findings

Our findings underscore the burden of long-term pulmonary complications in COVID-19 survivors, with significant implications for healthcare planning and resource allocation. The high prevalence of post-viral fibrosis and respiratory dysfunction highlights the need for comprehensive follow-up and multidisciplinary care. Early identification of high-risk patients, combined with

targeted interventions, could mitigate the long-term impact of COVID-19 on pulmonary health.

Future Directions

Further research is needed to elucidate the molecular mechanisms underlying post-viral fibrosis and identify potential therapeutic targets. Advances in imaging and biomarker studies could enhance early detection and personalized treatment strategies. Comparative studies across diverse populations and healthcare settings would provide valuable insights into regional variations and inform global health strategies.

Conclusion

This study highlights the significant burden of long-term pulmonary complications following COVID-19, including post-viral fibrosis and respiratory dysfunction, in a Bangladeshi cohort. The prevalence of fibrotic changes, persistent dyspnea, and reduced pulmonary function underscores the necessity of early identification and multidisciplinary management to improve outcomes and quality of life for survivors. Our findings align with global evidence while emphasizing regional disparities in healthcare access and comorbidity management. Further research should explore targeted interventions and molecular pathways to advance treatment strategies.

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