Original Article

Long-term outcome of pulmonary involvement in patients with coronavirus disease 2019: The role of high-resolution computed tomography and functional status – A prospective single-center observational study

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Abstract:

BACKGROUND: Since its first outbreak, coronavirus disease 2019 (COVID-19) has led to a great deal of published literature highlighting the short-term determinants of morbidity and mortality. Recently, several studies have reported radiological and functional sequelae from 3 months to 1 year among hospitalized COVID-19 survivors; however, long-term (more than 1 year) respiratory consequences in this population remain to be evaluated.

OBJECTIVE: To assess the long-term radiological and pulmonary function outcomes of patients with COVID-19 2 years after resolution of the initial infection.

METHODS: Hospitalized COVID-19 patients with moderate to severe disease who survived acute illness were included in this prospective and partially retrospective study. Clinical assessment, laboratory tests, high-resolution computed tomography scans, and pulmonary function tests (PFTs) were performed at baseline, followed by radiological and lung function assessments at 6 and 24 months.

RESULTS: Among 106 enrolled participants (mean age 62 ± 13.5 years; males: 61), 44 (41.5%) and 27 (25.4%) underwent radiological assessment at 6 and 24 months, respectively. Overall, 22.6% (24) of patients had residual radiological abnormalities. Overt fibrosis was observed in 12.2% of patients. Computed tomography disease severity and extent diminished significantly at 6 (13 ± 6, $P < 0.001$) and 24 months (11 ± 6, $P < 0.001$) from baseline. PFTs were performed in 65 (61.3%), 22 (20.7%), and 34 (32%) patients at baseline, 6 and 24 months, respectively. Impaired diffusion capacity (median diffusion capacity for carbon monoxide: 60%, interquartile range [IQR]: 51–80), restrictive lung defect (mean total lung capacity: 73.4% ± 18% predicted), and reduced exercise tolerance (median 6-min walk distance: 360 m, IQR: 210–400) were the predominant features at baseline. With the exception of exercise tolerance, a statistically significant improvement was observed in lung function parameters at the extended follow-up (2 years).

CONCLUSIONS: Hospitalized COVID-19 survivors are at increased risk of developing long-term pulmonary complications, including lung fibrosis. A protocol-based approach to the management of post-COVID-19 patients is mandatory to improve future outcomes.

Keywords:

Coronavirus disease 2019, long-coronavirus disease 2019, post coronavirus disease 2019 interstitial lung disease, postcoronavirus disease 2019 sequelae, pulmonary fibrosis

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Postcoronavirus disease 2019 (COVID-19) syndrome, long COVID-19 or postacute COVID-19 sequelae are persistent, recurring, or new-onset health problems 4–12 weeks after the initial COVID-19 infection.[1,2] The propensity of COVID-19 to affect multiple systems of the body and its severe, protracted clinical course during the acute phase predisposes survivors to long-term consequences.[3,4] Since the first report in which 87% of patients had persistent symptoms,[5] several meta-analyses and systematic reviews have estimated the prevalence of post-COVID-19 sequelae. However, significant heterogeneity exists which is partly attributed to a wide range of clinical settings in which studies were conducted; population studied (hospitalized vs. mixed), severity of disease (moderate vs. severe), clinical endpoints (symptoms vs. objective assessment such as computed tomography [CT] scan and/or pulmonary function tests [PFTs]), and follow-up duration (1 month–1 year or more).[3,4,6-10]

The lungs are the most commonly affected organs in acute COVID-19 infections. Diffuse alveolar injury, dysregulated host immune response, and persistent inflammation months after initial infection are some of the postulated mechanisms that contribute to the development of post-COVID-19 pulmonary sequelae.[11] Therefore, it is not surprising that dyspnea was the most commonly reported organ specific symptom with an estimated prevalence of 18%–35%.[4,6,7] Previous experience with coronavirus outbreaks (severe acute respiratory syndrome [SARS] and Middle East respiratory syndrome [MERS]) demonstrated persistent radiological and lung function impairment in terms of reduced diffusion capacity for carbon monoxide (DLCO) and reduced functional capacity (6-min walk distance [6MWD]) at the 1-year follow-up.[3,12] A 15-year follow-up study conducted on healthcare workers who survived SARS showed gradual improvement in both radiological and pulmonary function, with the effect most pronounced in the 1st year postrecovery.[13] Keeping in mind the phylogenetic similarity of SARS and MERS coronaviruses with COVID-19, long-term respiratory sequelae are expected. Whether these sequelae lead to progressive or regressive illness remains unclear.

Having already dealt with a similar coronavirus (MERS) outbreak in the past decade, Saudi Arabia holds a unique place among the list of countries facing pandemics. As of November 2022, 824,513 confirmed COVID-19 cases were recorded, with a mortality rate of 1.1%.[14] Despite the unprecedented and swift response of Saudi government in battle against COVID-19,[15] local observational studies have reported a high prevalence (36%–50%) of long-term, post-COVID-19 sequelae in months following the initial infection.[16-18] However, most of these studies have focused on persistent symptoms with limited objective evidence of respiratory impairment, such as imaging or lung function. Moreover, to the best of our knowledge, there is a paucity of published literature evaluating serial radiological and pulmonary function after 1 year. Therefore, the aims of this study were (1) to assess the radiological course and pulmonary function of patients with COVID-19 at 6–12 months interval for a period of 2 years from the time of initial infection, and (2) to assess the functional status of these patients using the 6MWD.

Methods

Study design

This was a single-center, prospective cohort study of hospitalized COVID-19 patients who were discharged and referred to the institutional, dedicated post-COVID-19 respiratory clinic from April 2020 to April 2021. Moreover, retrospective analysis of data (CT chest and/or PFTs) was also performed for those patients who were discharged within 3–6 months prior to study period and were prospectively followed at 6 and 24 months.

The study protocol was reviewed and approved by the Research and Ethics Committee of our institution.

Study population

All hospitalized patients older than 18 years with COVID-19 confirmed by reverse transcriptase-polymerase chain reaction in a respiratory tract sample were included if they had persistent respiratory symptoms after 8–12 weeks of initial infection.

We excluded patients with chronic obstructive pulmonary disease, interstitial lung disease, active malignancy with lung involvement, bronchiectasis, advanced heart failure, pulmonary hypertension, and pregnancy.

Data collection

Baseline visit (8–12 weeks post infection)

An extensive retrospective review of the medical records of enrolled patients was conducted, including demographic data, comorbid illnesses, smoking history, inpatient disease course, need for mechanical or noninvasive ventilation, medication history, and intensive care unit (ICU) and/or hospital length of stay. Laboratory parameters at the time of hospital admission included complete blood count, coagulation, renal and hepatic profiles, inflammatory markers (C-reactive protein, procalcitonin, ferritin, lactate dehydrogenase, D-dimer, interleukin-6), and N-terminal pro B-type natriuretic peptide.

Thorough clinical evaluation was undertaken at the baseline clinic visit, which included a detailed history, clinical examination, and review of laboratory parameters. Unenhanced high-resolution CT (HRCT) and PFTs were also reviewed, as described below.

Chest computed tomography evaluation and scoring

Two radiologists, who were blinded to the clinical data, systemically scored the CT images. Radiological abnormalities such as ground-glass opacities (GGOs), consolidation, interstitial thickening, bronchiectasis, crazy paving, coarse reticular pattern, parenchymal band, lymphadenopathy, and pleural effusion, as well as the extent of the lung lobes and segments were recorded. Pulmonary opacities in all five lobes were subjectively evaluated on chest CT, with scores of 0 (no involvement), 1 (<5% area affected), 2 (5%–25% area affected), 3 (25%–50% area affected), 4 (50%–75% area affected), and 5 (>75% area affected). The CT-severity score (CTSS) was calculated as the sum of the individual scores in five lung lobes, which ranged from 0 (no involvement) to 25 (maximum involvement) points.

Pulmonary function tests

All patients underwent spirometry (forced vital capacity [FVC] and forced expiratory volume in 1 s [FEV_1; best results of 3 successful attempts]), whole body plethysmography (total lung capacity [TLC] and residual volume), in accordance with the recommendations of the American Thoracic Society/European Respiratory Society[19,20] with a combination spirometer/plethysmograph (MasterScreen Body; Jaeger, Würzburg, Germany). The DLCO was measured using a single-breath technique (671178, Erich Jaeger Master screen PFT, GmbH D-9204 Hoechben, Germany). Data are expressed as percentages of predicted values. 6MWD was also requested for all patients, with or without supplemental oxygen, using the American Thoracic Society recommended criteria.

Follow-up assessment

The patients were followed up in the post-COVID-19 respiratory clinic at 6 months interval for a period of 2 years; however, after the 6-month visit, PFTs could not be performed for most of the patients due to technical difficulties in the pulmonary function lab. Therefore, the study protocol was modified and a final follow-up was conducted at 2 years.

Statistical analysis

Qualitative and quantitative variables were expressed as frequencies or absolute values with percentages (%) and mean ± standard deviations or as median and interquartile range (IQR), respectively. All measurements were assessed using a normality test. Associations between at least two qualitative or categorical variables were assessed using Chi-square test. Student's *t*-test and ANOVA variance were used for continuous variables with normal distribution. Comparisons of clinical and demographic characteristics between groups were performed using the two-sample Student's *t*-test or Mann–Whitney *U*-test, as appropriate. A two-sided $P < 0.05$ was considered statistically significant. All statistical analyses were performed using IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp.

Results

Between April 2020 and April 2021, 243 COVID-19 patients with persistent respiratory symptoms at the time of discharge were referred to the post-COVID-19 respiratory clinic. Ninety (37%) patients did not meet the study's inclusion criteria; 35 patients declined follow-up at our center, while 12 patients died during the study period and were excluded from the final analysis. Finally, a cohort of 106 patients (47%) was studied [Figure 1].

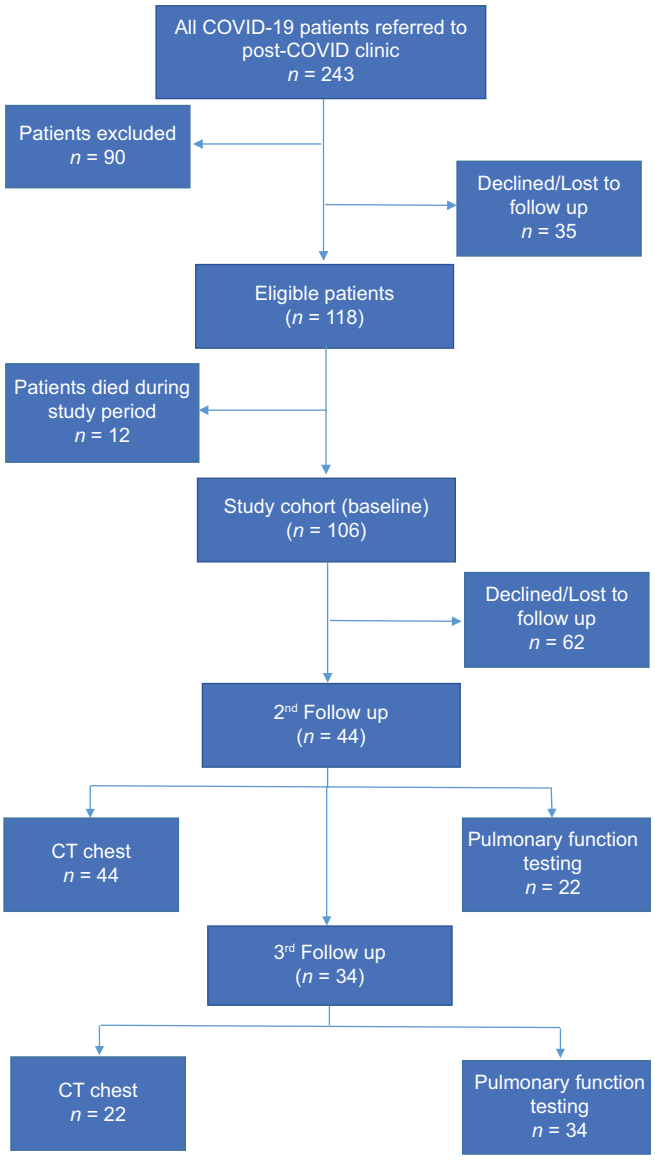

Figure 1: Distribution of study cohort

The baseline clinical and radiographic characteristics of the patients are detailed in Tables 1 and 2, respectively. The majority (57%) were middle-aged (mean age 62 ± 13.5), male patients with a mean body mass index (BMI) of 32 (±8). All patients had moderate (57%) to severe (39%) disease (4% were critically ill) at admission, of which 41 (39%) required ICU admission and 23 (21%) required mechanical ventilation. Diabetes mellitus was the most common comorbidity identified in 44% of the patients, while 27% had no significant underlying illness. The mean ICU and hospital lengths of stay were 13 (±8) and 17 (±13) days, respectively. Thirty-two (30%) patients were discharged with supplemental oxygen. All patients were prescribed corticosteroid therapy during their inpatient stay in accordance with hospital/local treatment guidelines for COVID-19 management; however, 28% of patients were given an extended duration of oral corticosteroids for a period of 6–8 weeks after discharge from the hospital.

At the first clinic visit (8–12 weeks postinitial infection), most patients (92%) complained of persistent symptoms, most notably cough (84%), dyspnea (83%), and fatigue (54%). While nine patients were asymptomatic, complete resolution of radiological findings was observed in only four patients. Multifocal GGOs were the most frequent radiological findings on chest CT (84%), followed by bronchiectasis (cystic, tubular,

Table 1: Baseline clinical, demographic and laboratory characteristics of study population

Characteristics	Study population (*n*=106)
Age (mean±SD), years	62±13.5
Male (n/%)/female (*n*/%)	61 (57.5)/45 (42.5)
BMI (mean±SD)	32±8
Smoking status	
Non-smoker (*n*/%)	75 (71)
Smoker (*n*/%)	31 (29)
Symptoms (baseline clinic visit)	
Cough (*n*/%)	89 (84%)
Dyspnea (*n*/%)	
mMRC I	9 (8)
mMRC II-III	56 (53)
mMRC IV	23 (22)
Fatigue (*n*/%)	54 (56)
Asymptomatic (*n*/%)	9 (8)
Comorbid illnesses	
None (*n*/%)	30 (27)
Diabetes mellitus (*n*/%)	47 (44)
Hypertension (*n*/%)	18 (17)
Ischemic heart disease (*n*/%)	4 (3.7)
Immunosuppressive treatment (*n*/%)	4 (3.7)
Chronic liver disease (*n*/%)	2 (2)
End stage renal disease (*n*/%)	2 (2)
Inpatient stay	
Ward (n/%)/ICU (*n*/%)	65 (61)/41 (39)
Mechanical ventilation (n/%)	23 (21)
Non-invasive ventilation (HFNC/NIPPV) (*n*/%)	22 (26)/9 (11)
ICU length of stay (mean±SD), days	13±8
Hospital length of stay (mean±SD)	17±13
Supplemental home oxygen (*n*/%)	32 (30)
Maintenance Corticosteroid therapy (*n*/%)	30 (28)
Inflammatory markers	
CRP (mean±SD) mg/L	109±72
Ferritin (mean±SD) ng/mL	1025±961
D-dimer (mean±SD) ng/mL	2994±4976
Interleukin-6 (mean±SD) ng/L	133±261

BMI=Body mass index, mMRC=Modified medical research council, ICU=Intensive care unit, HFNC=High flow nasal cannula, NIPPV=non-invasive positive pressure ventilation, CRP=C-reactive protein

Table 2: Baseline radiological characteristics of study population

	Population (*n*=106)
Radiological (HRCT chest) findings *n*/%	
Ground glass opacities	89 (84%)
Consolidation	34 (32%)
Interlobular septal thickening	50 (47%)
Bronchiectasis	61 (57%)
Crazy paving	5 (4%)
Air trapping	5 (4%)
Nodules	4 (3.7%)
Lymphadenopathy	4 (3.7%)
Atelectasis	4 (3.7%)
Complete resolution	4 (3.7%)
Dominant pattern (*n*/%)	*n*=102
Inflammatory	32 (31%)
Fibrosis	8 (8%)
Mixed	56 (55%)
Non-specific (atelectasis, parenchymal bands, mosaic pattern, nodules)	6 (6%)
CT severity score (CTSS)	*n*=102
Mean score±SD	15±6
Mild (1-7)	16 (15%)
Moderate (8-17)	52 (51%)
Severe (17-25)	34 (33%)

Table 3: Baseline Pulmonary function parameters

PFTs	*n*=65
FVC (absolute value, L) mean±SD	2.46±0.82
% predicted, mean±SD	72.5±16.6
FEV1 (absolute value, L) mean±SD	2.17±0.72
% predicted, mean±SD	82.4±17.1
FEV_1/FVC, %	88±8.1
TLC (absolute value, L) mean±SD	4.29±1.24
% predicted, mean±SD	73.4±18.5
DLCO	*n*=29
% predicted, median (IQR)	60 (51-80)
6MWD	*n*=19
Distance in meters, median (IQR)	360 (210-400)
% predicted, median (IQR)	68 (51-79)
Distance < LLN (*n*/%)	14 (73)
Borg dyspnea score post exercise, median (IQR)	1 (0-4)
Borg fatigue score post exercise, median (IQR)	1 (0-4)

traction) (57%), and interlobular septal thickening (47%). A mixed pattern of inflammation and fibrosis was observed in the majority of CT scans (55%), whereas predominant fibrotic changes (as evident by the presence of interlobular septal thickening, traction bronchiectasis, parenchymal distortion, and volume loss) were observed in eight patients as early as 8–12 weeks post infection. The findings were multifocal, with no predilection for a specific lung region. The severity scores (CTSS) for the baseline CT scans ranged from 5 to 25, with a mean score of 15 (±6). Although there was no significant association between sex, age, or BMI of patients and mean CTSS, patients with higher CTSS had significantly longer ICU and hospital lengths of stay ($P = 0.03$, $P < 0.001$). Patients who were mechanically ventilated and suffered from severe clinical and radiological disease during hospital admission had significantly higher mean CTSS than those who had moderate disease ($P = 0.04$) or did not require mechanical ventilation ($P = 0.01$).

Table 4: Radiological and lung function parameters at 6 and 24 months of follow-up

Clinical characteristics	6 months (*n*=44)	24 months (*n*=27)
Age (mean±SD), years	62±10.4	60±12.2
Gender (male/female)	22/22	12/15
CT findings, *n* (%)		
Ground glass opacities	32 (73)	13 (48)
Consolidation	2 (4)	1 (3)
Interlobular septal thickening	32 (73)	24 (89)
Traction bronchiectasis	23 (52)	13 (48)
Complete resolution	2 (4)	3 (11)
Dominant pattern		
Inflammatory	8 (18)	None
fibrotic	9 (20)	13 (48)
Mixed	25 (57)	11 (41)
Disease severity		
CTSS (mean±SD)	13±6	11±6
Mild (1–7)	11 (25)	6 (22)
Moderate (8–17)	21 (48)	15 (55)
Severe (17–25)	10 (22)	3 (11)
PFTs	*n*=22	*n*=34
FVC (mean±SD)		
Absolute (L)	2.8±0.82	2.72±1.02
Percentage predicted	77.3±15	84.2±21.2
FEV_1 (mean±SD)		
Absolute (L)	2.5±0.72	2.36±0.85
Percentage predicted	86.3±17.7	91.7±23
FEV_1/FVC (%)	88±0.06	87.5±5.9
TLC		
Absolute (L)	4.35±0.89	4.48±1.74
Percentage predicted	74.7±16.2	81.2±24
DLCO		
Percentage predicted, median (IQR)	96 (66–123)	88 (74–99)
6MWD median (IQR)		
Distance (m)	267 (240–294)	315 (240–390)
Percentage predicted	65 (56–78)	69 (61–82)
Borg dyspnea score post exercise	3 (1–4)	2 (0–4)
Borg fatigue score post exercise	1 (0–3)	2(0–3)

SD=Standard deviation, IQR=Interquartile range, DLCO=Diffusion lung capacity for carbon monoxide, TLC=Total lung capacity, FVC=Forced vital capacity, 6MWD=6-min walk distance, PFTs=Pulmonary function tests, FEV_1=Forced expiratory volume in 1 s, CTSS=CT-severity score

Table 3 summarizes the baseline PFT data that were available for 65 (61%) patients, while DLCO and 6MWD could only be performed in 29 (27%) and 19 (18%) patients, respectively. None of the patients had preadmission PFTs available for comparison. The most frequently observed abnormality was a reduction in DLCO (<80% predicted, median: 60%, IQR: 51–80) seen in 22 out of 29 patients (75%), followed by a mild reduction in FVC (<80% predicted, mean FVC 72.5% predicted [±16.6%]) and TLC (mean TLC: 73.4% predicted [±18%]) in 66% and 59% of patients, respectively. Female patients had significantly lower absolute FEV_1 ($P < 0.001$), FVC ($P < 0.001$), and TLC ($P = 0.001$) than male patients; however, no significant difference was observed when the predicted percentages were compared. The DLCO and 6MWD were also significantly lower in females than males ($P = 0.016$ and $P = 0.001$, respectively). ICU patients had significantly lower absolute (4.6 vs. 3.7, $P = 0.008$) and predicted (78 vs. 65, $P = 0.007$) TLC than non-ICU patients; however, there was no statistically significant difference between the absolute and predicted FEV_1, FVC, and DLCO values between the two cohorts.

All 19 patients with 6MWD had lower age-adjusted walk distances (<80% predicted), with a median walk distance of 360 m (IQR: 210–400). Nine patients were on supplemental home oxygen; however, only 2 patients experienced significant desaturation (>4%) upon exercise. Although ICU patients had a lower mean 6MWD (294 ± 77 m) than non-ICU patients (394 ± 108 m), the difference did not reach statistical significance ($P = 0.07$).

Table 4 shows radiological and lung function parameters at 6 and 24 months. At the 6-month follow-up, the majority of patients (58%) were either lost to follow-up or were asymptomatic; hence, declined further investigation. Among those (44/106) who underwent CT imaging, only 2 patients had radiological resolution. Although GGOs and consolidation were present in 32 out of 44 patients, fibrotic features were observed in 52% of patients, with overt fibrosis seen in 9 (20%) patients. Therefore, a combined inflammatory and fibrotic pattern was the predominant pattern at 6 months in 57% of the patients. According to the modified study protocol, the same cohort who had persistent changes at 6 months underwent follow-up 24 months after the baseline visit. Finally, 27 patients (25% of the entire cohort) underwent CT at 2 years. Twenty patients (74%) had stable disease,

4 (15%) patients showed disease progression from the 6-month follow-up CT scan, and only 3 (11%) patients had radiological resolution. Although 48% of patients had minimal GGOs, all patients with persistent radiological findings at 6 months (24/106) had interstitial abnormalities (23% of the whole cohort), and overt fibrosis (traction bronchiectasis, architectural distortion/volume loss) was observed in 12% (13/106) of patients. Overall, there was a statistically significant improvement in radiological disease extent and severity, as evidenced by differences in the mean CTSS at 6 (13 ± 6, $P < 0.001$) and 24 months (11 ± 6, $P < 0.001$) from baseline (15 ± 6). However, none of the clinical or laboratory parameters, such as age, sex, BMI, degree of breathlessness, ICU/hospital length of stay, baseline clinical or radiological disease severity, or laboratory markers, led to a significant difference among patients who had predominantly fibrotic disease compared to those who had mixed patterns at the 6 months or 24 months of follow-up.

PFTs were performed in 50% (22/44) and 77% (34/44) of the patients with abnormal CT scans at 6 and 24 months, respectively. All pulmonary function indices, except 6MWD, showed significant improvement at 6 months, with a similar trend at 2 years. The most striking finding was the statistically significant improvement in DLCO seen at 6 months (>80% predicted, median: 96%, IQR: 66–123) from baseline ($P = 0.021$) despite persistent radiological findings. Although no further improvement was observed at 24 months, the median DLCO remained >80% predicted in 72% of patients (median: 88% predicted, IQR: 74–99).

At 6 months, there was a significant improvement in spirometry and static lung volumes from the baseline. Mild restrictive abnormalities (FVC and TLC <80% predicted) were prevalent across the whole cohort; however, at 2 years of follow-up, majority of patients had FVC and TLC >80% predicted (62% and 53%, respectively), with a statistically significant difference from baseline (mean FVC: 84.2% ±21% predicted, $P < 0.001$, mean TLC: 81.2% ±24% predicted, $P = 0.004$) [Supplementary Table 1].

The 6MWD was available for only 18 out of 44 patients at 24 months, with a predicted distance <80% (median: 315 m, IQR: 240–390) seen in the majority (13/18, 72%) of patients. Due to the small number of patients, no significant correlation was found between lung function parameters and disease severity, radiological disease extent, and/or fibrosis.

Discussion

Available data regarding the duration of abnormalities detected on HRCT scans after recovery from COVID-19 are currently limited. Nonetheless, previous studies[21-27] have indicated that certain patients may exhibit persistent radiological and functional abnormalities that may last for several months after clinical recovery from COVID-19. The nature and duration of these abnormalities on HRCT scans can vary depending on factors such as the severity and duration of the initial infection as well as individual-specific factors.

In our study, we conducted a longitudinal assessment of the patients over a period of 24 months. This extended duration and multi-dimensional respiratory assessment makes our study one of the most comprehensive investigations regarding the evaluation of respiratory imaging and physiology in post-COVID-19 sequelae. Furthermore, our study is one of the few conducted in our region.

Our study revealed the prevalence of persistent radiological abnormalities in 23% (24/106) of patients, while only a small proportion (8%) had complete radiological resolution within 2 years. Moreover, overt fibrosis was observed in 13/27 (48%) patients (12% of the whole cohort), a prevalence lower than that in a recently published study with a 2-year longitudinal follow-up,[28] but somewhat similar to what Sanna *et al*. found at 15 months.[29] Although interstitial changes suggestive of early fibrosis were present as early as 12 weeks, inflammatory patterns (GGOs and consolidation) combined with interstitial changes were the predominant radiological features in the first 6 months, findings corroborated those of previously published studies.[22,24,26] Thereafter, the proportion of patients with fibrotic interstitial abnormalities increased from 20% (9/44) at 6 months to 89% (24/27) at 2 years, compared with inflammatory or mixed patterns. Furthermore, at 2 years, we identified four patients who had gradually progressive fibrosis, while the rest had stable disease when compared to 6 months. Our results are in contrast to those found by Han *et al*.[28] where the proportion of patients with fibrosis did not differ significantly between 6 and 24 months, and the majority of their patients showed complete radiological resolution. A possible explanation for this difference could be that the majority of our patients who reported subjective improvement between 1st and 2nd visit declined further follow-up and imaging studies.

Another significant finding was the progressive decline in severity and extent of radiological disease from baseline, as evidenced by a reduction in mean CTSS at 6 ($P < 0.001$) and 24 ($P < 0.001$) months, as well as from 6 to 24 months ($P < 0.0001$). These findings are in line with the data reported previously,[23,27,30] where reduction in severity was mostly attributed to improvement in GGOs and consolidation, demonstrating resolution of inflammation and alveolar re-expansion.[27]

In terms of lung function, all pulmonary function parameters, including diffusion capacity, showed significant improvement between 6 and 24 months signaling functional recovery, despite abnormal CT scans. Although the median DLCO was 88% predicted (IQR: 74–99), 28% of the patients had persistently impaired diffusion capacity at 24 months. A number of systematic reviews and meta-analyses have reported a reduction in DLCO to be the most prominent finding in functional COVID-19 sequelae[3,10,26,31] in the first 3–6 months postinfection. Parenchymal lung damage and microvascular thrombosis during acute infection are physiologically postulated mechanisms for impaired gas transfer.[31] Female sex, high inflammatory markers, CTSS, and severe acute COVID-19 infection were associated with impaired gas exchange in several studies.[21,22,26] Whether gas exchange improves significantly over time is a matter of debate, with some studies suggesting significant improvement from 6 months to 1 year,[22,27,28] whereas others have demonstrated persistently impaired DLCO.[21,32] In the current study, we found a significant improvement in the median DLCO at 6 months, which persisted until 2 years.

Our study has certain limitations. First, this study was limited to a single center and was hence prone to institutional bias. Second, the sample size is relatively small. Therefore, a robust correlation between certain clinical, demographic, and functional characteristics cannot be established. Third, the lack of a control group and absence of respiratory radio-physiological assessment of our patients before COVID-19 infection could potentially impact our results, as understanding the preexisting respiratory characteristics of the patients would provide a valuable context. Lastly, not all patients underwent the same assessments (for example, not all patients had PFTs and 6MWD), which resulted in missing data and affected the correlation between radiological and functional assessments.

Conclusions

Our study provides further evidence that long-term respiratory structural and functional impairment is a significant risk factor for people who are hospitalized with COVID-19. These findings emphasize the need for comprehensive long-term evaluations and appropriate management strategies for individuals with prolonged sequelae. Further research is warranted to better understand the underlying mechanisms and to evaluate the prognosis of these patients.

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Conflicts of interest
There are no conflicts of interest.

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Supplement Table 1: Radiological and Lung function parameters at baseline, 6 and 24 months follow-up

CT findings baseline	CT findings 6m	CT findings 24m	CTSS baseline	CTSS 6m	CTSS 24m	FVC baseline	FVC 6 m	FVC 24m	TLC baseline	TLC 6 m	TLC 24 m	DLCO baseline	DLCO 6m	DLCO 24 m	6MWD baseline	6MWD 6m	6MWD 24 m
GGOs, IT, traction bronchiectasis	Interstitial thickening	IT, traction bronchiectasis	21	15	15	1.6 (70%)	1.98 (77%)	2.41 (97%)	2.59 (59%)	3.13 (65%)	3.62 (78%)	-	62%	87%	210 (50%)	294 (67%)	330 (75%)
GGOs	GGOs, IT	IT, traction bronchiectasis	14.5	16	6	1.88 (77%)	-	2.08 (75%)	3.20 (71%)	-	3.27 (73%)	54%	-	-	-	-	-
GGOs, consolidation	GGOs, IT	IT	20	20	20	2.90 (80%)	-	4.10 (114%)	5.78 (82%)	-	5.89 (84%)	-	-	97	315 (68%)	-	395 (84%)
GGOs, IT	GGOs	clear	15	5	0	2.20 (87%)	-	2.5 (96.9%)	4.69 (105%)	-	4.21 (92%)	59%	-	75%	-	-	330 (81%)
GGOs, mosaic attenuation	GGOs	clear	14	6	0	3.22 (75%)	3.41 (80%	4.63 (108.4%)	4.83 (75%)	5.96 (90%)	6.1 (95%)	64%	78%	81%	-	-	420 (76%)
GGOs, consolidation	IT	-	22	10	-	3.12 (92%)	-	3.56 (98.2%)	6.18 (94%)	-	8.65 (118%)	-	-	-	-	-	385 (71%)
GGO, IT	GGOs, IT, traction bronchiectasis	IT, traction bronchiectasis	25	23	23	2.09 (76%)	2.32 (81%)	-	3.08 (66%)	3.48 (77%)	-	77%	98%	-	-	-	-
GGOs, consolidation	GGOs, consolidation	IT	19	15	11	1.5 (40%)	2.02 (55%)	2.65 (73%)	-	3.18 (49.3%)	4.06 (72%) -	47%	-	72%	-	-	285 (69%)
GGOs, IT	GGOs, IT	IT, traction bronchiectasis	25	10	10	1.52 (47%)	2.10 (81%)	2.59 (100%)	2.50 (57%)	3.63 (94%)	3.15 (77%)	-	-	75%	255 (51%)	-	300 (78%)
GGOs, consolidation	GGOs, IT	IT, traction bronchiectasis	17	15	15	1.53 (45%)	1.73 (55%)	3.08 (97%)	3.31 (53%)	3.88 (66%)	5.73 (95%)	56%	-	139%	390 (95%)	-	345 (86%)
GGOs, consolidation	GGOs, IT	-	20	10	-	2.35 (54%)	2.52 (58%)	3.6 (85.3%)	4.06 (60%)	3.88 (57%)	5.47 (81%)	-	59%	97%	-	-	390 (84%)
consolidation, GGOs, traction bronchiectasis	IT, traction bronchiectasis	IT, traction bronchiectasis	16	15	15	2.4 (54%)	2.97 (68%)	3.45 (86%)	3.05 (42%)	4.33 (60%)	7.2 (104%)	43%	56%	90%	-	-	375 (79%
GGOs, traction bronchiectasis	IT, traction bronchiectasis	IT, traction bronchiectasis	16	15	14	1.85 (43%)	2.92 (64%)	2.92 (65%)	4.07 (51%)	4.10 (55%)	-	53%	104%	-	-	-	-
GGOs, IT, traction bronchiectasis	IT, traction bronchiectasis	IT, bronchiectasis	18	18	-	1.62 (61%)	2.23 (79%	2.46 (92%)	1.8 (36%	4.26 (87%)	4.34 (92%)	-	-	67%	-	-	270 (68%)
GGOs, IT, bronchietasis	IT, bronchiectasis	IT, bronchiectasis	17	16	14	2.4 (59%)	2.62 (64%)	3.5 (82.4%)	3.64 (57%)	4.09 (63%)	5.54 (82%)	61%	82%	118%	-	-	460 (88%)

IT: Interstitial Thickening, GGOs: Ground glass opacities, CTSS: CT severity score, FVC: Forced vital capacity, TLC: Total lung capacity, DLCO: Diffusion lung capacity for carbon monoxide, 6MWD: six-minute walk distance