Chronic Parenchymal Lung Changes after COVID-19 Infection

Abdelfattah Touman  
King Abdullah Medical City  
https://orcid.org/0000-0002-6143-4326

Mohammed Khayat  
(✉️ m-khayat@live.com)  
King Abdullah Medical City  
https://orcid.org/0000-0003-0775-7535

Adeeb Bulkhi  
UQU College of Medicine: Umm Al-Qura University College of Medicine

Mutaz Khairo  
King Abdullah Medical City

Wael Alyamani  
King Abdullah Medical City

Ahmad aldobyany  
King Abdullah Medical City

Nabil Ghaleb  
King Abdullah Medical City

Hadeel Ashi  
King Abdullah Medical City

Mohammed Alsobai  
King Abdullah Medical City

Eid Alqurashi  
King Abdullah Medical City

Research Article

**Keywords:** Interstitial lung disease, Long COVID, Post-COVID fibrosis

**DOI:** https://doi.org/10.21203/rs.3.rs-750050/v1

**License:** ☒️  This work is licensed under a Creative Commons Attribution 4.0 International License.  
Read Full License
Abstract

**Background:** Persistent parenchymal lung changes are an important long-term sequela of COVID-19. There are limited data on the disease characteristics and trajectories. This study aims to evaluate persistent COVID-19-related parenchymal lung changes after 10 weeks of acute viral pneumonia and to identify its risk factors.

**Methods:** This was a retrospective case-control observational study involving 38 COVID-19 confirmed cases using nasopharyngeal swab reverse-transcriptase-polymerase-chain-reaction (RT-PCR) at King Abdullah Medical City (KAMC) hospital, Makkah. Patients were recruited from the Post-COVID interstitial lung disease (ILD) clinic. Referral to this clinic was based on the pulmonology consultants’ assessment of hospitalized patients suspected of developing COVID-19-related ILD changes during hospitalization.

**Measurements and Main Results:** Nineteen patients with persistent parenchymal lung changes after 10 weeks of the acute illness (group-1) were compared with 19 control patients referred for assessment of post-COVID-19 ILD and had accelerated clinical and/or radiological features (group-2). Group-1 was found to have more severe clinical and radiological disease, with higher peak value of inflammatory biomarkers. Two risk factors were identified, NLR >3.13 at admission increases the odds ratio (OR) of chronic parenchymal changes by 6.42 and 13.09 in the univariate and multivariate analyses, respectively. Invasive mechanical ventilation had a more profound effect with ORs of 5.92 and 44.5 in the univariate and multivariate analyses, respectively.

**Conclusion:** Herein, persistent parenchymal lung changes were observed in several patients 10 weeks after acute COVID-19 infection. We found that only receiving invasive mechanical ventilation and NLR >3.13 at admission were strong risk factors for persistent parenchymal lung changes.

**Summary Of Research Impact**

- Persistent parenchymal lung changes have been demonstrated in several patients 10 weeks after acute COVID-19 infection.
- Ground glass opacities remain the predominant lung changes after 10 weeks of acute COVID-19 pneumonia.
- Clinical characteristics that independently predict persistent parenchymal lung changes included neutrophil-to-lymphocyte ratio (NLR) above 3.13 at admission, and application of invasive mechanical ventilation.

**Background**

The novel coronavirus disease was first detected in December 2019 in Wuhan, China. In February 2020, the World Health Organization (WHO) announced that the coronavirus disease was caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and it was named COVID-19. This shortly led to
a global pandemic. By May 2021, more than 150 million confirmed cases and approximately 3 million deaths were reported worldwide [1]. Since the pandemic started, there has been an overflow of studies targeting disease pathophysiology, treatment, and prevention, and some have been published. However, many aspects and the nature of the disease, including long-term pulmonary sequelae, are not well understood. Early reports described persistent symptoms after acute COVID-19 infection [2][3]. These symptoms and organ dysfunction were not limited to the lungs but included psychological, cardiovascular, neurological, hematological, and other system disorders [3], [4]. Persistent parenchymal lung changes, in particular, have been described in several observational studies.[5]–[7]. Nevertheless, there are limited data on the disease characteristics and trajectories. This study aimed to elaborate on the clinical and radiological features of parenchymal pulmonary sequelae and factors that may contribute to the development of fibrosis post-acute COVID-19 pneumonia.

**Methods**

**I. Study design and patient selection**

This retrospective case-control observational study involved 38 COVID-19 confirmed cases using nasopharyngeal swab RT-PCR at King Abdullah Medical City (KAMC), Makkah-Saudi Arabia. Patients were recruited from the Post-COVID-19 interstitial lung disease (ILD) clinic. Referral to this clinic was based on a pulmonologist’s assessment of hospitalized patients suspected of developing COVID-19-related ILD changes during hospitalization.

At the Post-COVID ILD clinic, detailed medical history and physical examination were performed. Laboratory and physiological assessments were requested for all patients; however, follow-up chest CT was requested for patients with significant residual disease, such as patients with severe symptoms who still required oxygen at home in order to maintain oxygen saturation for more than two months after discharge and those in whom the prednisolone dose could not be tapered down. According to evidence of persistent COVID-19-related parenchymal lung changes, the 38 selected patients were divided into two groups. Those patients who had undergone follow-up chest CT, at least 10 weeks after the first positive RT-PCR swab, and had residual parenchymal lung diseases were included in the case group "Group 1". The control group included patients with earlier clinical and/or radiological resolution.

Inclusion criteria included all adults (age >12 years) and RT-PCR-confirmed COVID-19 infection with radiological evidence of pneumonia. We excluded patients diagnosed with fibrotic or other structural lung diseases prior to having COVID-19 infection. Patients who were lost to follow-up after discharge or judged to need a follow-up chest CT and missed their radiology appointments were also excluded.

Baseline patient characteristics, including age, sex, smoking history, and obesity, comorbidities, and other clinical variables related to acute COVID-19 disease, such as inflammatory markers, treatment intervention, and intensive care unit (ICU) admission, were collected from electronic the patients’ records.
II. Chest CT image protocol and interpretation

CT scans were acquired without ECG gating on a 64-slice multidetector CT (Siemens SOMATOM Sensation 64) with a $64 \times 0.625$ mm collimation and a spiral pitch factor of 1.3. Scans were obtained in the craniocaudal direction, supine position, and during end-inspiration without the administration of an intravenous contrast agent with a standard dose scanning protocol. For patients who had a clinical suspicion of pulmonary embolism (PE), additional CT pulmonary angiography was conducted. Axial reconstructions were performed with a slice thickness of 1.5 mm.

Two radiologists, each with 6 years of experience, reviewed all chest CT images. The images were reviewed independently, and any discrepancies were resolved by consensus. There was no major disagreement between the radiologists’ interpretations.

For each of the two patient groups, the CT examinations were evaluated for the following characteristics: (1) CT severity scores (CT-SS) for initial and follow-up CT as described by Li et al. [8]; (2) ground-glass opacities and consolidations; and (3) presence of fibrotic lesions (traction bronchiectasis, parenchymal bands, honeycombing, and reticulations).

The CT severity scores were based on a visual quantitative evaluation of the percentage of involvement in each lobe as well as the overall lung. The severity scores were classified as none (0%), minimal (1–25%), mild (26–50%), moderate (51–75%), or severe (76–100%), with corresponding scores of 0, 1, 2, 3, or 4, respectively. The CT-SS was reached by summing the five lobe scores (ranging from 0 to 20).

In the “case group,” the CT performed during acute illness was termed “the initial CT,” and CT performed 10 weeks after the first RT-PCR was termed “the follow-up CT.” However, follow-up CT images were not obtained in most patients in the “control group” as they showed significant clinical improvement; thus, the first CT performed during acute illness was termed as “the initial CT,” and the latest CT subsequently performed (not necessarily after 10 weeks of the acute illness) was termed “the follow-up CT.”

III. Definitions of clinical status

1. Disease severity
   i. **Moderate**: RT-PCR-confirmed COVID-19 pneumonia without any severe or critical criteria
   ii. **Severe**: RT-PCR-confirmed COVID-19 pneumonia with any of the following: respiratory rate $\geq 30$/min, blood oxygen saturation $\leq 93\%$, PaO$_2$/FiO$_2$ ratio $<300$, or radiological lung infiltration $>50\%$ of the lung field as judged on chest CT
   iii. **Critical**: RT-PCR-confirmed COVID-19 pneumonia with any of the following: respiratory failure requiring non-invasive or invasive ventilation, sepsis or septic shock, altered consciousness, or multi-organ failure
IV. Statistical analysis

Statistical analyses were performed using STATA/IC version v16.1 software (StataCorp LLC, TX, USA). For normally distributed variables, means and standard deviations (SDs) were used to describe continuous variables, and frequencies and percentages were used for categorical variables. Non-normally distributed variables were described using median and interquartile ranges. Comparisons across groups were made using chi-square or Fisher's exact test for categorical variables and one-way ANOVA or Kruskal-Wallis test as appropriate for continuous variables.

Logistic regression was used to evaluate risk factors associated with post-COVID-19 ILD. Multivariate models were adjusted for age, sex, smoking history, body mass index (BMI) >30, and asthma to eliminate possible confounding factors. The variables were selected based on previous studies and clinical relevance. Statistical significance was set at P < 0.05.

Results

The patients' demographic and clinical characteristics are presented in Table 1. Patients with persistent ILD were predominantly males (73.68%); however, this difference was not statistically significant between the two groups. Age, BMI, smoking history, and comorbidity were not statistically significant.
Table 1
Baseline characteristics table.

| Demographic data and comorbidities                  | Control (Group-2) No. 19 | Case (Group-1) No. 19 | P-value |
|-----------------------------------------------------|--------------------------|-----------------------|---------|
| Age (years) (SD)                                    | 54.36 (12.14)            | 59.74 (13.82)         | 0.33    |
| Gender: Male (%)                                    | 10 (52.63)               | 14 (73.68)            | 0.18    |
| Smoking History (%)                                 | 4 (21.05)                | 4 (21.05)             | 0.65    |
| Body mass index > 30 (%)                            | 11 (57.89)               | 10 (52.63)            | 0.74    |
| History of diabetes (%)                             | 10 (52.63)               | 11 (57.89)            | 0.74    |
| History of hypertension (%)                         | 10 (52.63)               | 11 (57.89)            | 0.74    |
| History of chronic heart disease (%)                | 5 (26.32)                | 5 (26.32)             | 0.99    |
| History of renal impairment (%)                     | 3 (15.79)                | 2 (10.53)             | 0.63    |
| History of chronic obstructive pulmonary disease (%)| 1 (5.26)                 | 0 (0)                 | 0.31    |
| History of Asthma (%)                               | 4 (21.05)                | 3 (15.79)             | 0.68    |
| History of active malignancy (%)                    | 1 (5.26)                 | 3 (15.79)             | 0.29    |

Inflammatory Biomarker Characteristics

| ESR (SD)                                            | 69.48 (36.33)            | 82.21 (40.92)         | 0.24    |
| CRP (IQ)                                            | 7.2 (4.9–12.7)           | 12.45 (5.92–16.85)    | 0.23    |
| Procalcitonin (IQ)                                  | 0.15 (0.11–0.58)         | 0.27 (0.09–0.43)      | 0.78    |
| D-dimer (IQ)                                        | 1.24 (0.63–2.36)         | 2.00 (0.78–7.88)      | 0.21    |
| LDH (SD)                                            | 363 (301–565)            | 480 (348–666)         | 0.22    |
| Ferritin (IQ)                                       | 535 (262–1345)           | 711 (263–1407)        | 0.84    |
| Lymphopenia at admission (%)                        | 8 (42.11)                | 8 (42.11)             | 0.10    |
| Admission NLR > 3.13 (%)                            | 7 (36.84)                | 15 (78.95)            | **0.01**|
| High Trop I during hospitalization (%)              | 3 (16.67)                | 2 (10.53)             | 0.59    |
| RDW > or equal to 14.1 (%)                          | 12 (63.16)               | 14 (73.68)            | 0.49    |
|                          | Control (Group-2) No. 19 | Case (Group-1) No. 19 | P-value |
|--------------------------|--------------------------|-----------------------|---------|
| RDW value (IQ)           | 14.7 (12.9–16.3)         | 15.5 (13.7–17.3)      | 0.14    |

At admission, patients with a neutrophil to lymphocyte ratio of above 3.13 at admission were more prevalent in cases than in the control group (78.95% vs. 36.84%), and this was statistically significant (p = 0.01). Patients in group 1 had a higher peak value of inflammatory biomarkers, including ESR, CRP, PCT, LDH, and ferritin compared with those in the control group. However, these were not statistically significant; the same applies to the D-dimer peak admission value.

Overall, 84.3% of cases had severe to critical disease in the control group compared with 100% in the case group (p = 0.10). About two-thirds of the patients in both the groups were admitted to the ICU: 52.63% in the control group and 68.42% in case group. The number of days in the ICU, pharmacological treatment, and oxygen therapy other than mechanical ventilation were also comparable. Mechanical ventilation was strongly associated with persistent parenchymal lung changes; other hospital interventions and clinic-related clinical data are shown in Table 2. The initial CT-SS was higher in the cases group than in the control group (13.06 and 9.58, respectively) (p = 0.043). However, after adjusting for age in the univariate and multivariate analysis, they were no longer significant with p-values of 0.05 and 0.08, respectively. Ground-glass opacities were detected in all cases, followed by parenchymal bands as the second most prevalent abnormality in nearly 80% of cases. None of the cases had a honeycomb appearance on chest CT imaging.
|                                     | Control No.19 | Case No.19 | P-value |
|-------------------------------------|---------------|------------|---------|
| **Admission-related clinical data** |               |            |         |
| ICU admission (%)                   | 10 (52.63)    | 14 (73.68) | 0.31    |
| **Disease severity (%)**            |               |            |         |
| Moderate                            | 3 (15.79)     | 0 (0.00)   | 0.10    |
| Severe                              | 9 (47.37)     | 7 (36.84)  | 0.99    |
| Critical                            | 7 (36.84)     | 12 (63.16) | 0.28    |
| **Received medications**            |               |            |         |
| Interferon (%)                      | 5 (26.32)     | 5 (26.32)  | 0.99    |
| Lopinavir/ritonavir (%)             | 3 (15.79)     | 4 (21.05)  | 0.68    |
| Ribavirin (%)                       | 1 (5.26)      | 1 (5.26)   | 0.99    |
| Convalescent plasma (%)             | 0 (0.00)      | 3 (15.79)  | 0.07    |
| Systemic steroid (%)                | 13 (68.42)    | 14 (73.68) | 0.72    |
| Tocilizumab (%)                     | 6 (31.58)     | 11 (57.89) | 0.10    |
| **Ventilatory support**             |               |            |         |
| Nasal cannula /Face mask (%)        | 13 (68.42)    | 17 (89.47) | 0.11    |
| High flow nasal cannula (%)         | 6 (31.58)     | 8 (42.11)  | 0.50    |
| BiPAP (%)                           | 3 (15.79)     | 4 (21.05)  | 0.67    |
| Mechanical ventilator (%)           | 1 (5.26)      | 8 (42.11)  | 0.008   |
| HFOV (%)                            | 1 (5.26)      | 2 (10.53)  | 0.55    |
| **Discharge-related clinical data** |               |            |         |
| Systemic steroid after discharge (%)| 9 (47.37)    | 15 (78.95) | 0.043   |
| Oxygen at discharge (%)             | 4 (21.05)     | 7 (36.84)  | 0.28    |
| Readmission within 4 weeks of discharge (%) | 2 (11.11) | 5 (26.32)  | 0.23    |
| Weeks on systemic steroid (SD)      | 4.00 (4.77)   | 9.11 (8.43)| 0.03    |
| Weeks on home oxygen (IQ)           | 0.00 (0.00–4.00) | 0 (0.00–1.00) | 0.19 |
The radiological severity score and other persistent parenchymal abnormalities on follow-up chest CT are shown in Table 3 and illustrated in Fig. 1.

Table 3

| Initial CT-SS (SD) | Control (No.17) | Cases (No. 18) | P-value | Univariate OR | P-value | Multivariate OR | P-value |
|-------------------|-----------------|----------------|---------|---------------|---------|-----------------|---------|
|                   | 9.58 (4.17)     | 13.06 (5.45)   | 0.043   | 1.16 (0.99-1.34) | 0.05    | 1.45 (0.98-1.34) | 0.08    |

Adjusting for age (best fitted model)

Imaging characteristics of cases (Group-1) on the follow-up chest CT

| Follow-up CT performed Weeks (SD) | 14.474 (4.55) |
|----------------------------------|---------------|
| Initial CT severity score (SD)   | 13.06 (5.45)  |
| Follow-up CT severity score (SD) | 9.84 (5.75)   |
| Traction bronchiectasis (%)      | 11 (57.89)    |
| Parenchymal bands (%)            | 15 (78.95)    |
| Honeycombing (%)                 | 0.00 (0.00)   |
| Reticulations (%)                | 10 (52.63)    |
| Ground glass (%)                 | 19 (100)      |
| Consolidation (%)                | 3 (15.79)     |

| CT severity score (SD)           | 9.84 (5.75)   |

Table 4 shows the univariate and multivariate analyses of both groups for the possible risk factors of post COVID-19 fibrosis. Our analysis showed that a neutrophil-to-lymphocyte ratio (NLR) of >3.13 and receiving invasive mechanical ventilation increased the odds ratio (OR) of chronic parenchymal changes. The OR were 6.42 and 13.09, respectively, in the univariate analysis and 5.92 and 44.5, respectively, in the multivariate analysis. Male sex, obesity, and comorbidity had a modest increased OR but were statistically insignificant. Other inflammatory markers and treatments are presented in Table 4.
Table 4
Univariate and Multivariate analysis table.

|                         | Univariate OR     | P-value | Multivariate OR          | P-value |
|-------------------------|-------------------|---------|--------------------------|---------|
| Age (years)             | 1.034 (0.981–1.090) | 0.210   | 1.048 (0.981–1.119)      | 0.167   |
| Gender (male)           | 2.520 (0.646–9.833) | 0.183   | 3.44 (0.72–16.48)        | 0.123   |
| Smoking History         | 1.000 (0.210–4.758) | 0.999   | 0.84 (0.13–5.67)         | 0.859   |
| Body mass index > 30    | 0.808 (0.225–2.909) | 0.744   | 1.36 (0.29–6.36)         | 0.697   |
| History of diabetes     | 1.24 (0.29–5.36)   | 0.500   | 0.82 (0.18–3.83)         | 0.804   |
| History of hypertension | 1.237 (0.344–4.454) | 0.744   | 1.052 (0.213–5.195)      | 0.951   |
| History of chronic heart disease | 1.000 (0.236–4.238) | 0.999   | 0.935 (0.160–5.459)      | 0.940   |
| History of renal impairment | 0.627 (0.092–4.259) | 0.633   | 0.559 (0.053–5.898)      | 0.630   |
| History of asthma       | 0.703 (0.134–3.677) | 0.677   | 0.92 (0.13–6.60)         | 0.942   |
| History of active malignancy | 3.38 (0.24–186.91) | 0.302   | 1.93 (0.11–32.85)        | 0.216   |
| Lymphopenia at admission | 2.979 (0.789–11.248) | 0.107   | 2.719 (0.617–11.982)     | 0.186   |
| Admission NLR > 3.13    | 6.429 (1.517–27.244) | **0.012** | 5.928 (1.243–28.273)     | **0.026** |
| High Trop I during hospitalization | 0.588 (0.086–4.009) | 0.588   | 0.311 (0.037–2.604)      | 0.282   |
| ICU admission           | 1.950 (0.520–7.312) | 0.322   | 1.232 (0.217–7.009)      | 0.814   |
| RT-PCR positivity for more than 14 days | 0.791 (0.206–3.032) | 0.733   | 0.686 (0.141–3.328)      | 0.640   |
| Hydroxychloroquine      | 1.000 (0.175–5.720) | 0.999   | 0.653 (0.093–4.566)      | 0.667   |
| Favipiravir             | 2.187 (0.516–9.271) | 0.288   | 2.509 (0.521–12.069)     | 0.251   |
| Interferon              | 1.000 (0.236–4.238) | 0.999   | 0.884 (0.186–4.208)      | 0.877   |
| Condition                              | Univariate OR (95% CI) | P-value | Multivariate OR (95% CI) | P-value |
|----------------------------------------|------------------------|---------|--------------------------|---------|
| Lopinavir/ritonavir                    | 1.422 (0.272–7.438)    | 0.677   | 0.902 (0.143–5.669)      | 0.912   |
| Ribavirin                              | 1.000 (0.058–17.249)   | 0.999   | 1.125 (0.046–27.285)     | 0.942   |
| Systemic steroid                       | 1.292 (0.317–5.275)    | 0.721   | 1.399 (0.289–6.757)      | 0.676   |
| Tocilizumab                            | 2.979 (0.789–11.248)   | 0.107   | 2.648 (0.593–11.834)     | 0.202   |
| Nasal cannula/ Face mask               | 3.923 (0.678–22.705)   | 0.127   | 2.914 (0.346–24.543)     | 0.325   |
| High flow nasal cannula                | 1.576 (0.417–5.950)    | 0.502   | 1.148 (0.201–6.559)      | 0.877   |
| BiPAP                                  | 1.422 (0.272–7.438)    | 0.677   | 1.129 (0.190–6.709)      | 0.894   |
| Mechanical ventilator                  | 13.091 (1.436–119.338) | **0.023** | 44.542 (2.498–794.378)   | **0.010** |
| HFOV                                   | 2.118 (0.176–25.549)   | 0.555   | 2.708 (0.148–49.436)     | 0.501   |
| Respiratory bacterial infection         | 4.800 (0.483–47.682)   | 0.181   | 4.453 (0.377–52.610)     | 0.236   |
| Other systemic infection                | 1.000 (0.210–4.758)    | 0.999   | 0.877 (0.166–4.630)      | 0.877   |
| Systemic steroid after discharge       | 4.167 (1.003–17.305)   | **0.049** | 3.034 (0.651–14.132)     | 0.157   |
| Oxygen supplementation                 | 2.187 (0.516–9.271)    | 0.288   | 1.627 (0.331–7.990)      | 0.550   |
| Readmission within 4 weeks of discharge | 2.857 (0.477–17.110)   | 0.250   | 1.778 (0.211–14.960)     | 0.597   |
| ESR                                    | 1.009 (0.992–1.027)    | 0.316   | 1.005 (0.987–1.024)      | 0.573   |
| CRP                                    | 1.061 (0.962–1.169)    | 0.237   | 1.061 (0.944–1.191)      | 0.320   |
| Procalcitonin                          | 0.767 (0.384–1.532)    | 0.452   | 0.833 (0.444–1.560)      | 0.567   |
| D-dimer                                | 1.063 (0.950–1.190)    | 0.286   | 1.063 (0.945–1.195)      | 0.309   |
|                          | Univariate OR       | P-value  | Multivariate OR      | P-value |
|--------------------------|---------------------|----------|----------------------|---------|
| LDH                      | 1.002 (0.999–1.005) | 0.216    | 1.002 (0.998–1.006)  | 0.280   |
| Ferritin                 | 1.000 (0.999–1.001) | 0.774    | 1.000 (0.999–1.001)  | 0.418   |
| Number of ICU days       | 1.062 (0.989–1.141) | 0.098    | 1.067 (0.983–1.159)  | 0.122   |
| Weeks on systemic steroid| 1.121 (1.007–1.248) | **0.038**| 1.126 (1.001–1.267)  | **0.048**|
| Weeks on home oxygen     | 1.231 (0.936–1.618) | 0.137    | 1.214 (0.925–1.595)  | 0.163   |

Adjusting for age, gender, smoking history, BMI > 30, Asthma

### Discussion

Persistent parenchymal lung changes beyond acute COVID-19 infection are one of the most important post-COVID-19 sequelae. Disease characteristics and trajectories have not been well studied. In this study, we followed-up with 38 patients, 10 weeks after COVID-19 infection, and compared a group of patients with persistent parenchymal lung changes with a group of patients who had clinical resolution of symptoms. We found that ground-glass opacity (GGO) was the predominant lung change after 10 weeks. Clinical characteristics that independently predict a protracted course for pulmonary parenchymal changes included a NLR of > 3.13 at admission and invasive mechanical ventilation.

Following previous outbreaks of coronaviruses, long-term pulmonary sequelae have been reported[9], [10]. In a 12-month follow-up study of 311 patients with SARS, 21.5% of patients had lung fibrosis 65 days after discharge[11]. Das et al. reported that 13 out of 36 patients with Middle East respiratory syndrome (MERS) had persistent parenchymal changes 32–230 days after being discharged[12]. Regarding COVID-19, persistent symptoms, impaired diffusion capacity of the lung for carbon monoxide (DLCO), and persistent radiological findings beyond acute illness have been reported [13]. Trinkmann et al. reported that 113 out of 246 patients remained symptomatic after a mean follow-up period of 68 days; dyspnea was the most common symptom (32%) [14]. In Wuhan, a study showed impairment of DLCO after 90 days of discharge in 54% of patients [15]. In Norway, a multi-center prospective study reported that one-fourth of the patients had persistent CT findings on follow-up 3 months after discharge from acute COVID-19 hospitalization, and ICU admission was reported to be a risk factor.[16]. From the cases referred by the pulmonology consultants to follow-up of post-COVID-19 ILD, 19 cases confirmed using chest CT showed prolonged parenchymal abnormalities after at least 10 weeks of the acute infection. These cases were matched with 19 cases that showed early clinical and radiological recovery.
The pathogenesis beyond the development of lung fibrosis in COVID-19 survivors is not clear. It is likely that SARS-CoV-2 binds and interacts with angiotensin-converting enzyme (ACE)-2, which increases transforming growth factor beta (TGF β1) and connective tissue growth factor (CTGF) levels, which may result in the development of fibrosis through the activation of fibrosis-related genes [17]. Surfactant abnormality and alveolar type-2 (AT2) cell injury result from the interaction between environmental factors, such as viruses and genetic factors, causing alveolar collapse, and repeated injury from ventilation could explain the progression to ventilator-induced lung injury (VILI) and lung fibrosis [18]. Evidence has shown that the most persistent ILD post-COVID-19 is reported in severe and critical cases [16], [19]–[21]. This raises the suspicion that ventilation-induced lung injury (VILI) and fibrosis following mechanical ventilation in ARDS has a major impact on the pathogenesis of post-COVID-19 ILD [18], [22]. Our study showed that receiving invasive mechanical ventilation had the highest impact on the likelihood of developing prolonged parenchymal changes. It increases the odds ratio (OR) of chronic parenchymal changes by 13.09 and 44.5 in the univariate and multivariate analyses, respectively.

Regarding disease severity, admission to the ICU and length of stay in the intensive care were not found to impact parenchymal lung sequelae; none of the medications administered for acute illness had an impact. However, CT-SS on initial chest CT was found to be higher in cases than in the control group, reflecting more radiologically severe disease in Group-1. After adjusting for age, the OR was found to be 1.16 (0.99–1.34), P = 0.05 and 1.45 (0.98–1.34), P = 0.08 in the univariate and the multivariate analysis, respectively.

A NLR of ≥ 3.13 was found to be an independent risk factor for severe and critical COVID-19 infection [23]. In this study, NLR was demonstrated to be a strong predictor of persistent parenchymal lung changes regardless of COVID-19 disease severity. There may be a role for increased neutrophils or decreased lymphocytes in disease pathogenesis and this requires further investigation.

In patients with idiopathic pulmonary fibrosis (IPF), a study has shown that a red cell distribution width (RDW) more than 14.1 was shown to be a negative prognostic factor as it correlates with lower forced vital capacity (FVC) and DLCO compared with IPF patients with normal RDW [24]. Increased RDW can be used as an indirect marker of hypoxemia. We did not find a difference in the percentage of patients who had RDW values above 14.1 between the groups. The absolute RDW value was also not different. We selected the value measured at the date of hospital discharge to allow time for acute illness-related hypoxemia to impact the RDW value.

Most of the reported lung fibrosis following MERS-CoV were observed in patients that were admitted for longer days in the ICU, elderly patients, and those with higher LDH levels [12]. The Swiss COVID-19 lung study evaluated pulmonary functions and radiological findings at four months of discharge and found that impaired DLCO was the strongest factor associated with previous severe to critical disease [19]. In this study, days of ICU admission, older age, and LDH level did not correlate with post-COVID-19 persistent parenchymal lung changes, in contrast to what was observed in MERS-CoV[12]. Moreover, we found that
prolonged viral shedding beyond 14 days had no direct impact on the development of persistent parenchymal lung changes after acute COVID-19 infection.

**Limitations**

It is important to acknowledge the limitations of our study, which includes its retrospective design and the limited number of patients. We did not perform chest CT for all control cases; however, clinical resolution of symptoms mirrors radiological changes resolution based on previous studies [21].

**Conclusion**

In this study, persistent parenchymal lung changes were observed in a number of patients 10 weeks after acute COVID-19 infection. We found that only receiving invasive mechanical ventilation and a NLR of > 3.13 at admission, are strong risk factors for persistent parenchymal lung changes. We also showed that neither the clinical nor the initial radiological severity of the acute illness predict the outcome of patients with COVID-19, and that no medication received during the acute illness altered the disease course. None of the medications received during the acute phase of the illness altered the disease course.

**Abbreviations**

NLR: neutrophil-to-lymphocyte ratio; ILD: interstitial lung disease; RT-PCR: reverse-transcriptase-polymerase-chain-reaction; ICU: intensive care unit; CT-SS: CT severity score; BMI: body mass index; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; PCT: Procalcitonin; LDH: Lactate dehydrogenase; OR: odds ratio; IPF: idiopathic pulmonary fibrosis; RDW: red cell distribution width; DLCO: diffusion capacity of the lung for carbon monoxide; SARS: severe acute respiratory syndrome; MERS: Middle East respiratory syndrome; ARDS: acute sever respiratory distress syndrome; ACE: angiotensin-converting enzyme; TGF β 1: transforming growth factor beta; CTGF: connective tissue growth factor; AT2: alveolar type-2; VILI: ventilator-induced lung injury.

**Declarations**

**Ethics approval and consent to participate**

The Institutional Review Board of King Abdullah Medical City (KAMC) approved this study (approval number: 21-763). Written consents was not required by IRB due to the retrospective nature of the study. The study protocol conformed to the ethical guidelines of the 1975 Helsinki Declaration.

**Consent for publication**

Not applicable.
Availability of data and material

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Funding:

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Competing interests

All authors declare that they have no competing interests.

Author contributions:

AT designed and supervised the study. AT & MK contributed in protocol development, data collection, interpretation of the analysed data & manuscript writing. AB performed the statistical analyses and data interpretation. MK & WA were responsible of radiological review, chest CT scoring and radiological data entry. HA, MA, AA, EA & NG involved in data collection and entry as well as manuscript editing. All authors reviewed and approved the final version of manuscript.

Acknowledgements:

We acknowledge the commitment and sacrifice of all health care providers through the COVID-19 pandemic and the suffering of our patients as well as in their families.

References

1. 2020. WHO COVID-19 Dashboard. Geneva: World Health Organization, “https://covid19.who.int/,” WHO COVID-19 Dashboard. Geneva: World Health Organization, 2020. https://covid19.who.int/ (accessed May 04, 2021).
2. “section_43,” A. May 04, 2021. [Online]. Available: https://www.covid19treatmentguidelines.nih.gov/.
3. Lopez-Leon S, et al., “More than 50 Long-term effects of COVID-19: a systematic review and meta-analysis Correspondence to,” doi: 10.1101/2021.01.27.21250617.
4. Nalbandian A, et al. Post-acute COVID-19 syndrome. Nat Med. Mar. 2021. doi:10.1038/s41591-021-01283-z.
5. Yu M, Liu Y, Xu D, Zhang R, Lan L, Xu H. “Prediction of the Development of Pulmonary Fibrosis Using Serial Thin-Section CT and Clinical Features in Patients Discharged after Treatment for COVID-19 Pneumonia,” Korean Journal of Radiology, 21, 6, 2020, doi:10.3348/kjr.2020.0215.

6. Wang Y, et al., “Temporal Changes of CT Findings in 90 Patients with COVID-19 Pneumonia: A Longitudinal Study,” Radiology, 296, 2, Aug. 2020, doi:10.1148/radiol.2020200843.

7. Pan F, et al., “Time Course of Lung Changes at Chest CT during Recovery from Coronavirus Disease 2019 (COVID-19),” Radiology, 295, 3, Jun. 2020, doi:10.1148/radiol.2020200370.

8. Li K, et al. CT image visual quantitative evaluation and clinical classification of coronavirus disease (COVID-19). Eur Radiol. 2020;30(8):4407–16. doi:10.1007/s00330-020-06817-6.

9. Ahmed H, et al., “Long-term clinical outcomes in survivors of severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) coronavirus outbreaks after hospitalisation or ICU admission: A systematic review and meta-analysis,” Journal of Rehabilitation Medicine, vol. 52, no. 5. Foundation for Rehabilitation Information, May 01, 2020, doi: 10.2340/16501977-2694.

10. Hui DS, et al. Impact of severe acute respiratory syndrome (SARS) on pulmonary function, functional capacity and quality of life in a cohort of survivors. Thorax. May 2005;60(5):401–9. doi:10.1136/thx.2004.030205.

11. Xie L, et al. Dynamic changes of serum SARS-Coronavirus IgG, pulmonary function and radiography in patients recovering from SARS after hospital discharge. Respir Res. 2005;6:1–7. doi:10.1186/1465-9921-6-5.

12. Das K, et al., “Follow-up chest radiographic findings in patients with MERS-CoV after recovery,” Indian Journal of Radiology Imaging, 27, 3, 2017, doi:10.4103/ijri.IJRI_469_16.

13. Sonnweber T, et al., “Cardiopulmonary recovery after COVID-19 – an observational prospective multicenter trial,” Eur Respir J, p. 2003481, Apr. 2020, doi:10.1183/13993003.03481-2020.

14. Trinkmann F, et al., “Residual symptoms and lower lung function in patients recovering from SARS-CoV-2 infection,” Eur Respir J, 2003002, 2021, doi:10.1183/13993003.03002-2020.

15. Follow-up M, et al., “Early View Original article Diffusion Capacity Abnormalities for Carbon Monoxide in Patients with COVID-19 At Three-,” 2020.

16. Lerum TV, et al., “Dyspnoea, lung function and CT findings three months after hospital admission for COVID-19,” Eur Respir J, p. 2003448, Apr. 2020, doi:10.1183/13993003.03448-2020.

17. Xu J, Xu X, Jiang L, Dua K, Hansbro PM, Liu G. SARS-CoV-2 induces transcriptional signatures in human lung epithelial cells that promote lung fibrosis. Respir Res. 2020;21(1):1–12. doi:10.1186/s12931-020-01445-6.

18. Albert RK, Smith B, Perlman CE, Schwartz DA, “Is Progression of Pulmonary Fibrosis due to Ventilation-induced Lung Injury?,” American Journal of Respiratory and Critical Care Medicine, vol. 200, no. 2. American Thoracic Society, pp. 140–151, 2019, doi: 10.1164/rccm.201903-0497PP.

19. Guler SA, et al., “Pulmonary function and radiological features four months after COVID-19: first results from the national prospective observational Swiss COVID-19 lung study,” Eur Respir J, p. 2003690, Apr. 2021, doi:10.1183/13993003.03690-2020.
20. Ojo AS, Balogun SA, Williams OT, Ojo OS, “Pulmonary Fibrosis in COVID-19 Survivors: Predictive Factors and Risk Reduction Strategies,” *Pulmonary Medicine*, vol. 2020. Hindawi Limited, 2020, doi: 10.1155/2020/6175964.

21. Myall KJ, et al. Persistent Post-COVID-19 Inflammatory Interstitial Lung Disease: An Observational Study of Corticosteroid Treatment. *Annals of the American Thoracic Society*. May 2021. doi:10.1513/annalsats.202008-1002oc.

22. Cabrera-Benitez NE, et al., “Mechanical ventilation-associated lung fibrosis in acute respiratory distress syndrome: A significant contributor to poor outcome,” *Anesthesiology*, vol. 121, no. 1. Lippincott Williams and Wilkins, pp. 189–198, 2014, doi: 10.1097/ALN.0000000000000264.

23. Liu J, et al., “Neutrophil-to-lymphocyte ratio predicts severe illness patients with 2019 novel coronavirus in the early stage,” *medRxiv* medRxiv Feb 12, 2020, doi:10.1101/2020.02.10.20021584.

24. Karampitsakos T, et al. Increased monocyte count and red cell distribution width as prognostic biomarkers in patients with Idiopathic Pulmonary Fibrosis. *Respir Res.* Dec. 2021;22(1):140. doi:10.1186/s12931-021-01725-9.

**Figures**
Figure 1

Representative CT scan of severe COVID-19 infection in the case group. A and B show the initial chest CT, while C and D show the follow-up CT images after 10 weeks. These images show significant improvement with residual minimal patchy ground-glass opacities, thickening of the interlobular septa, and linear opacities in both lungs.
Figure 2

Representative CT scan of moderate COVID-19 infection in the control group. A and B show the initial chest CT images with patchy ground-glass opacities, thickened interlobular septa, and focal consolidations in both lungs. C and D show that these lesions resolved in the follow-up CT.