

## CT FINDINGS IN “POST-COVID”: RESIDUA FROM ACUTE PNEUMONIA OR “POST-COVID-ILD”?

*Stefanie Meiler<sup>1</sup>, Florian Poschenrieder<sup>2</sup>, Arno Mohr<sup>2</sup>, Quirin Strotzer<sup>1</sup>, Gregor Scharf<sup>1</sup>, Janine Rennert<sup>1</sup>, Christian Stroszczynski<sup>1</sup>, Michael Pfeifer<sup>3</sup>, Okka W. Hamer<sup>1,4</sup>*

<sup>1</sup>Regensburg University Medical Center, Department of Radiology, Regensburg, Germany; <sup>2</sup>Hospital Donaustauf, Department of Pneumology, Donaustauf, Germany; <sup>3</sup>Hospital Barmherzige Brüder, Department of Pneumology, Regensburg, Germany; <sup>4</sup>Hospital Donaustauf, Department of Radiology, Donaustauf, Germany

**Abstract.** The aim of this study was to evaluate if CT findings in patients with pulmonary Post Covid syndrome represent residua after acute pneumonia or if SARS-CoV 2 induces a true ILD. Consecutive patients with status post acute Covid-19 pneumonia and persisting pulmonary symptoms were enrolled. Inclusion criteria were availability of at least one chest CT performed in the acute phase and at least one chest CT performed at least 80 days after symptom onset. In both acute and chronic phase CTs 14 CT features as well as distribution and extent of opacifications were independently determined by two chest radiologists. Evolution of every single CT lesion over time was registered intraindividually for every patient. Moreover, lung abnormalities were automatically segmented using a pre-trained nnU-Net model and volume as well as density of parenchymal lesions were plotted over the entire course of disease including all available CTs. 29 patients (median age 59 years, IQR 8, 22 men) were enrolled. Follow-up period was 80–242 days (mean 134). 152/157 (97%) lesions in the chronic phase CTs represented residua of lung pathology in the acute phase. Subjective and objective evaluation of serial CTs showed that CT abnormalities were stable in location and continuously decreasing in extent and density. The results of our study support the hypothesis that CT abnormalities in the chronic phase after Covid-19 pneumonia represent residua in terms of prolonged healing of acute infection. We did not find any evidence for a Post Covid ILD.

**Key words:** COVID-19, pneumonia, ILD, Long Covid

### Introduction

There is growing evidence that COVID-19 can cause persisting symptoms long-lasting after the acute phase (1–7). Terms like “Post Covid” and

“Long Covid” have been introduced to describe this phenomenon (7, 8), and first attempts to define this symptom-complex have been made (9). At the moment, Post Covid is defined as symptoms developing during or after an infection consistent with COVID-19 which continue for more than 12 weeks and cannot be explained otherwise (9–11). Meanwhile several studies have been published reporting on the CT and functional findings 3–12 months after acute COVID-19 (2, 4, 12–14). However, important points have so far not been addressed. Most notably there is an ongoing debate if persisting parenchymal pathologies are residua after SARS-CoV-2

Received: 22 February 2023 - Accepted: 20 May 2023

Stefanie Meiler, MD  
University Hospital Regensburg  
Franz-Josef-Strauss-Allee 11  
93053 Regensburg, Germany  
Phone: 0049941/9447410  
E-mail: stefanie.meiler@ukr.de

pneumonia or if COVID-19 triggers an autoimmune process which induces a true, potentially fibrotic and progressive interstitial lung disease (11, 15-19). The latter hypothesis is fueled by the evidence of autoantibodies found in patients with COVID-19, rheumatic manifestations and by the fact that autopsy studies identified a vasculitis/endotheliitis in COVID-19 pneumonia (20-25).

The purpose of this study was the evaluation of patients suffering from Post Covid with special focus on the question if CT findings in Post Covid rather represent residua after acute pneumonia or if COVID-19 induces a true interstitial lung disease.

## Material and Methods

### *Study design*

This retrospective study was approved by the institutional ethics committee. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Written informed consent was waived.

Inclusion period was May 2020 to March 2021. All patients who presented in a dedicated Post Covid outpatient clinic of a secondary care hospital specialized on lung diseases and of a tertiary care university hospital during the inclusion period were screened. Inclusion criteria were status post RT-PCR confirmed COVID-19 pneumonia and availability of at least one chest CT performed in the acute phase as well as a at least one CT performed at least 80 days after symptom onset. For every eligible patient the picture archiving and communication system (PACS, Syngo Imaging, Siemens, Erlangen, Germany) and Radiology Information System (RIS, Nexus.medRIS, Version 8.42, Nexus, Villingen-Schwenningen, Germany) were also searched for chest CT scans which were acquired before the acute COVID-19 episode. The latest of these earlier scans was also included into the analysis in order to determine pre-existing lung lesions. These pre-existing lung lesions were regarded as not related to COVID-19 during further analysis.

### *CT image acquisition*

The CTs were acquired on two scanners (128-slice Somatom Definition AS, 128-slice Definition FLASH, both Siemens Healthcare, Erlangen, Germany). The CT protocol was as follows: automatic tube voltage selection with a reference tube voltage of 120 kV, automatic tube current modulation with a reference mAs between 20 – 110, primary slice thickness 0.6 mm, multiplanar reformations (MPR) in the axial plane with a slice thickness of 1 mm in lung kernel and soft tissue kernel, sagittal and coronal MPRs with a slice thickness of 1 mm in lung kernel. As for acute phase scans, intravenous contrast material was administered according to the individual patient's clinical situation. In total, 59 % (17/29) of acute phase scans were contrast enhanced and 41 % (12/29) non-enhanced. As for chronic phase scans application of intravenous contrast material depended on the anticoagulation status: CT was performed without intravenous contrast in case the patient was anticoagulated and with contrast if the patient was not anticoagulated. In total, 48 % (14/29) of chronic phase scans were contrast enhanced and 52 % (15/29) non-enhanced. As for the contrast enhanced scans, Iohexal (Accupaque 350, GE Healthcare) was administered in a weight-adapted dose, but not more than 70 ml. Flow rate was 3 or 4 ml/s.

### *Subjective image analysis*

In case of several CT scans per patient in the acute phase, all scans were evaluated by a senior resident (XX) regarding extent of lung involvement. In order to capture the maximum of parenchymal injury the scan with the maximum extent of involved lung volume was selected for detailed analysis. In case of several scans per patient in the chronic phase the latest CT was selected for detailed analysis. The acute phase and chronic phase CT scans selected for detailed analysis were independently reviewed by two senior cardiothoracic radiologists (YY and ZZ) with 20 and 15 years of experience. Analysis was performed with the acute phase and chronic phase CTs displayed side by side on a PACS workstation. The two observers' independent analyses were compared afterwards and any disagreement was resolved by consensus. Readers were not aware of any clinical or functional findings.

### *Parameters for individual CT analysis*

The Fleischner Society definition of CT features were applied when appropriate (26). The term “bronchial dilatation” instead of „bronchiectasis“ was intentionally used in order to encompass potentially reversible and irreversible disease. Right heart strain was reported when the short axis diameter of right ventricle was larger than that of left ventricle or the diameter of the pulmonary trunk was  $\geq 3$  cm.

The affected lung lobes and the distribution of opacifications in the axial plane were registered. The extent of pulmonary opacifications was assessed subjectively according to a 5-point score (no abnormalities: 0, 1-5% of lung volume affected: 1, 6-24%: 2, 26-50%: 3, 51-75%: 4, 76-100%: 5).

### *Parameters for comparison of acute phase CT with chronic phase CT*

The chronic phase scan was compared with the acute phase scan in every patient side by side. For every single parenchymal abnormality in the chronic phase scan, it was recorded if there had been an abnormality at the same location in the acute phase scan or if the abnormality in the chronic phase scan had appeared “de novo”. If a corresponding pathology was present in the acute phase scan any transformation of CT features from acute to chronic was registered (e.g., consolidation in the acute phase scan transforms into GGO in the chronic phase scan). In case of “de novo” lesions all CT scans eventually acquired in between the selected acute phase and chronic phase scans were evaluated in order to identify if there had been an interim development of a lung pathology at the respective location. If there was a chest CT scan available which had been acquired before the acute COVID-19 episode this scan was thoroughly evaluated by both radiologists in order to distinguish COVID-associated lung abnormalities from non-COVID-associated pre-existing abnormalities.

### *Objective image analysis*

Percentage of pathologically altered lung tissue and mean lung tissue density were assessed objectively for all consecutive chest CTs of each patient acquired after the onset of COVID-19 symptoms

(i.e. all acute phase and all chronic phase CTs). A custom routine was implemented using Python 3.8.12. Lung lobes were automatically segmented from the structural scans using the lungmask python library (27). Lung lesions were automatically segmented using a pre-trained nnU-Net (28). Model weights (available from <https://zenodo.org/record/4635822>) were based on the COVID-19 Lung CT Lesion Segmentation Challenge 2020 (29). Segmentations were visually verified and manually corrected where needed using ITK-SNAP (version 3.8.0) (30). The percentage of pathological lung tissue was calculated as the volume of COVID-19 pathology divided by the total lung volume taken from the anatomical segmentations for each patient at each timepoint. A Gaussian smoothing algorithm was applied.

### *Statistical analysis*

Age is presented as a median (IQR) and all categorical variables as absolute and relative frequencies. Statistical analysis was done applying the McNemar test. Results with a type I error  $<0.05$  were considered significant. All analyses were performed using Microsoft Excel, version 16.47.1.

## **Results**

### *Characteristics of the cohort*

Overall, 130 patients presented in the Post Covid outpatient clinic during the inclusion period. 29 patients fulfilled the inclusion criteria. The study population consisted of 22 male (76 %) and 7 female (24 %) patients, aged from 42 to 75 years (median 59 years, IQR 8). 72 % (21/29) of patients had preexisting comorbidities (Table 1).

A total of 87 CT scans were performed in the 29 study patients. Two scans per patient were chosen for detailed analysis as described above. The selected (= maximum of parenchymal involvement) acute phase CT was acquired with a mean of 24 days (SD 18.8) after symptom onset, the selected (= latest) chronic phase CT with a mean of 134 days (range 80 – 242 days, SD 39.5) after symptom onset. In 8 patients (28 %) chronic phase CTs were acquired longer than 170 days after symptom onset. In 11 patients chest CTs performed between the selected acute phase CT and the latest chronic phase CT were available (1 CT

**Table 1.** Patients' characteristics.

parameter	patients (n=29), no. (%)
<b>age (years)</b>	59 (IQR 8)
<b>gender</b>	
male	22 (76)
female	7 (24)
<b>comorbidities</b>	
hypertension	12 (41)
obesity	5 (17)
obstructive sleep apnea syndrome	5 (17)
hypercholesterolemia	4 (14)
hyperuricemia	4 (14)
sarcoidosis	2 (7)
coronary heart disease	2 (7)
lung fibrosis	2 (7)
asthma	2 (7)
peripheral arterial occlusive disease	2 (7)
chronic cardiac failure, diabetes, granulomatosis with polyangiitis, emphysema, COPD, reflux esophagitis, hyperthyroidism, multiple myeloma, post ARDS	each 1 (3)
<b>smoking history</b>	8 (28)
<b>hospitalization during acute phase</b>	27 (93)
mean hospitalization time (d)	39 (SD 40.6)
<b>admitted to general ward</b>	8 (30)
mean time on ward (d)	14 (SD 9.9)
<b>admitted to ICU</b>	19 (70)
mean ICU time (d)	35 (39.5)
<b>symptoms at follow-up</b>	
exertional dyspnea	15 (52)
fatigue	9 (31)
cough	8 (28)
muscle weakness	6 (21)
concentration difficulties	4 (14)
thoracic pain	3 (10)
taste dysfunction	2 (7)
paresthesia	2 (7)
diarrhea, headache, lack of appetite, dizziness, joint pain, paresis	each 1 (3)

COPD = chronic obstructive pulmonary disease, ARDS = acute respiratory distress syndrome, d = days, ICU = intermediate care unit

in 6 patients, 2 CTs in 4 patients, 3 CTs in 1 patient). In 9 of 29 (31 %) patients chest CT scans prior to acute COVID-19 were available (among those one patient with pre-existing sarcoid and two patients with pre-existing fibrotic lung disease).

## Results of subjective image analysis

### *Acute phase scan*

In the acute phase scans, GGO (100 %, 29/29) and consolidation (86 %, 25/29) were the most frequent CT features (figure 1). Lesions were always bilateral (100 %, 29/29). For further detail see table 2.

### *Chronic phase scan*

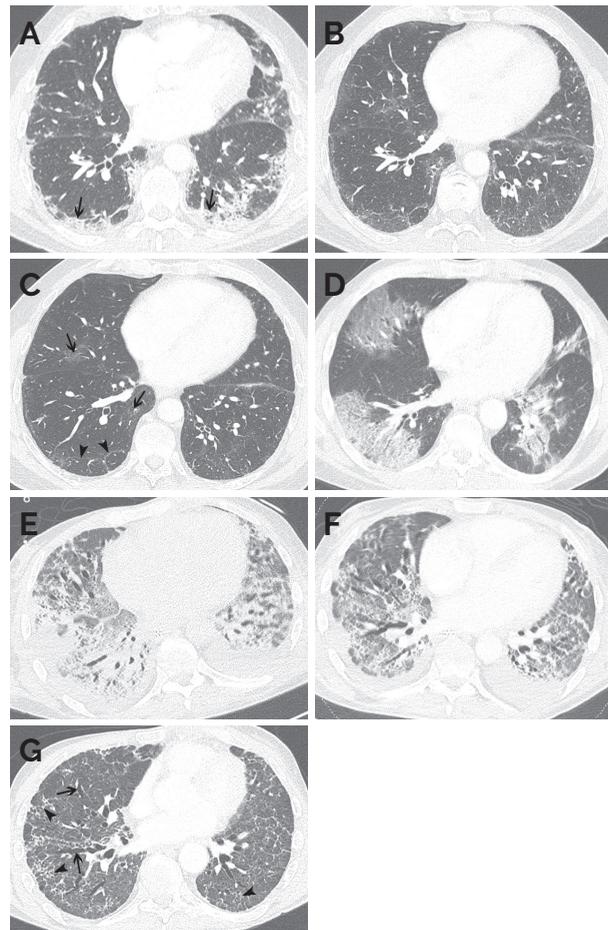
2 (7 %) of chronic phase scans were unremarkable. 27 (93 %) chronic phase scans showed at least one single abnormality. GGO still was the most frequently seen CT feature (86 %, 25/29) (table 2, figure 1). Consolidation was present in a significantly lower percentage than in the acute phase (17 %, 5/29). Crazy paving was not present anymore. Bronchial dilatation and bronchial wall thickening were observed in 52 % (15/29) and 31 % (9/29), respectively (figure 1). Linear opacities (76 % (22/29) and reticulation (38 %, 11/29) were significantly more frequent than in the acute phase (figure 1). In one single case only (3 %) honeycombing was seen. A few patients revealed to have nodules (14 %, 4/29) or cysts (7 %, 2/29). Pleural thickening was found in 31 % (9/29). For further detail see table 2.

### *Evolution of CT findings from acute phase CT to chronic phase CT*

All in all 157 separate parenchymal lesions were recorded in the 29 chronic phase CT scans. Anatomic coregistration revealed that 97 % (152/157) of these lesions had been preceded by an abnormality at the same location in the acute phase scan. In detail, GGO was seen 57 times in the chronic phase scan and was preceded in the acute phase scan by GGO in 22/57 observations (38.5 %), by consolidation in 18/57 observations (31.5 %), by crazy paving in 6/57 observations (10.5 %), by plate-like opacities in 6/57 observations (10.5 %) and by linear opacities in 2/57 cases (4 %). 3 observations of GGO appeared de novo (5 %). Consolidation was present four times in the chronic phase scan and was preceded in the acute phase scan by consolidation in three cases (75 %) and by a cyst in one case (25 %). Fibrosis (= bronchiectasis and/or irregular reticulation and/or honeycombing) was seen 29 times in the chronic phase scans

**Table 2.** Imaging findings.

CT findings	acute phase (n=29), no. (%)	chronic phase (n=29), no. (%)	p-value
<b>CT signs</b>			
consolidation	25 (86)	5 (17)	<0.001
crazy paving	9 (31)	0	0.008
round shape of opacification	9 (31)	0	0.008
sharp margin of opacification	24 (83)	9 (31)	<0.001
geographic shape of opacification	17 (59)	2 (7)	<0.001
plate-like opacification	16 (55)	6 (21)	0.02
linear opacification	14 (48)	22 (76)	0.03
bronchial dilatation	14 (48)	15 (52)	1
bronchial wall thickening	7 (24)	9 (31)	0.68
honeycombing	0	1 (3)	1
reticulation	4 (14)	11 (38)	0.02
nodules	4 (14)	4 (14)	0.68
cysts	3 (10)	2 (7)	1
pleural effusion	10 (34)	3 (10)	0.05
pleural thickening	9 (31)	9 (31)	0.72
lymphadenopathy	14 (48)	0	<0.001
signs of right heart strain	5 (17)	7 (24)	0.68
pulmonary artery embolism	2 (12)*	0	n.a.
<b>distribution</b>			
bilateral	29 (100)	25 (86)	0.13
unilateral	0	2 (7)	0.48
right upper lobe	26 (90)	22 (76)	0.13
right middle lobe	25 (86)	21 (72)	0.13
right lower lobe	29 (100)	26 (90)	0.25
left upper lobe	26 (90)	22 (76)	0.13
left lower lobe	28 (97)	25 (86)	0.37
predominantly peripheral	19 (66)	16 (55)	0.37
predominantly central	1 (3)	0	1
predominantly anterior	0	1 (3)	1
predominantly posterior	18 (62)	12 (41)	0.11
<b>extent of lung involvement</b>			
0	0	2 (7)	
1 (1-5%)	3 (10)	11 (38)	
2 (6-24%)	7 (24)	3 (10)	
3 (26-50%)	5 (17)	4 (14)	
4 (51-75%)	6 (21)	3 (10)	
5 (76-100%)	8 (28)	6 (21)	
GGO = ground glass opacity. *out of 17 contrast-enhanced acute phase scans			



**Figure 1.** Course of CT findings. a) – c) Axial contrast-enhanced CT scans of a 63 yo male a) in the acute phase 23 days after symptom onset, b) in the chronic phase 97 days after symptom onset and c) in the chronic phase 154 days after symptom onset. In the acute phase consolidation and less so GGO are present predominantly in the periphery of the posterior lung. Large parts of the opacifications are sharply demarcated (arrows). During follow-up the opacifications are stable in location but continuously decreasing in extent and density. Residual GGO (arrows) and linear opacities (arrowheads) remain. Also bronchial wall thickening is seen. There are no de novo abnormalities. d)–f) Axial contrast-enhanced and non-enhanced CT scans of a 56 yo male d) in the acute phase 5 days after symptom onset, e) in the acute phase 55 days after symptom onset and f) 63 days after symptom onset as well as g) in the chronic phase 175 days after symptom onset. The CTs in the acute phase show a pattern characteristic for COVID-19 pneumonia turning into a pattern of ARDS. During follow-up GGO and consolidation resolve while bronchial dilatation (arrows) and reticulations (arrowheads) develop. There are no de novo abnormalities.

**Table 3.** Evolution of CT findings from acute phase to chronic phase CTs (per every single lesion in chronic phase CTs).

lesions in chronic phase CTs	preceding lesions at the same location in acute phase CTs (no. (%))							
	GGO	consolidation	crazy paving	plate-like opacification	linear opacification	cysts	bronchiectasis	de novo
GGO	22/57 (38.5)	18/57 (31.5)	6/57 (10.5)	6/57 (10.5)	2/57 (4)	-	-	3/57 (5)
consolidation	-	3/4 (75)	-	-	-	1/4 (25)	-	-
fibrosis*	16/29 (55)	12/29 (41)	-	-	-	-	1/29 (3)	-
linear opacification	18/54 (33)	18/54 (33)	4/54 (7)	9/54 (17)	3/54 (6)	-	-	2/54 (4)
plate-like opacification	2/6 (33)	3/6 (50)	-	1/6 (17)	-	-	-	-
nodules	2/4 (50)	2/4 (50)	-	-	-	-	-	-
cysts	2/3 (67)	-	-	-	-	1/3 (33)	-	-

GGO = ground glass opacity. \* defined as honeycombing and/or bronchiectasis and/or irregular reticulation

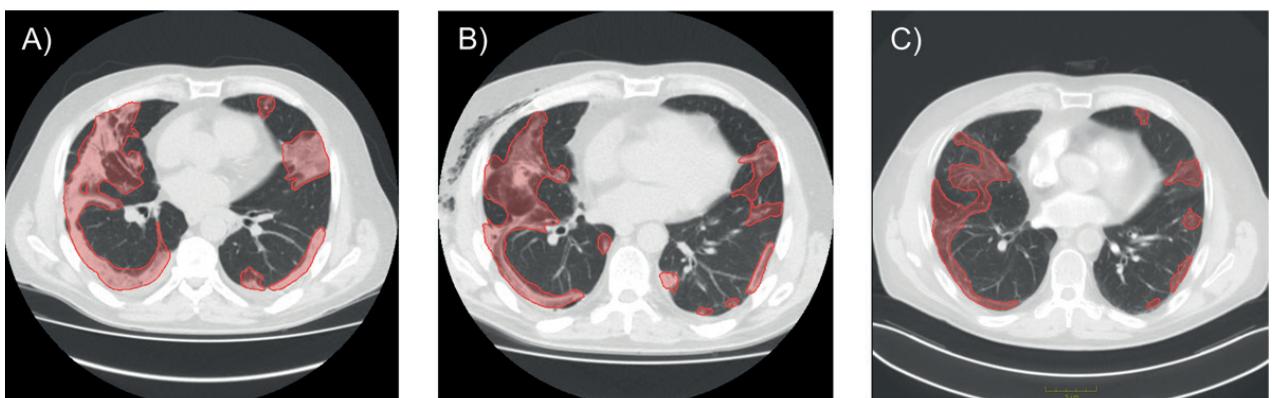
and was preceded in the acute phase scans by GGO in 16/29 observations (55 %), by consolidation in 12/29 observations (41 %) and by bronchiectasis in 1/29 observations (3 %). Linear opacifications were registered 54 times and had been preceded by GGO in 18/54 observations (33 %), by consolidation in 18/54 observations (33 %), by crazy paving in 4/54 observations (7 %), by plate-like opacities 9/54 times (17 %) and by linear opacities 3/54 times (6 %). 2 linear changes appeared de novo (4 %). We noticed 6 observations of plate-like opacities in the chronic phase scans and they were preceded by GGO in 2 cases (33 %), by consolidation in 3 cases (50 %) and by plate-like opacities in 1 single case (17 %). In 4 observations, nodules were present and they were preceded by GGO and consolidation in 2 cases each (50 %). Cysts were seen in 3 cases, with GGO (2/3,

67 %) and cysts (1/3, 33 %) to be found at the very same place in the acute phase scan.

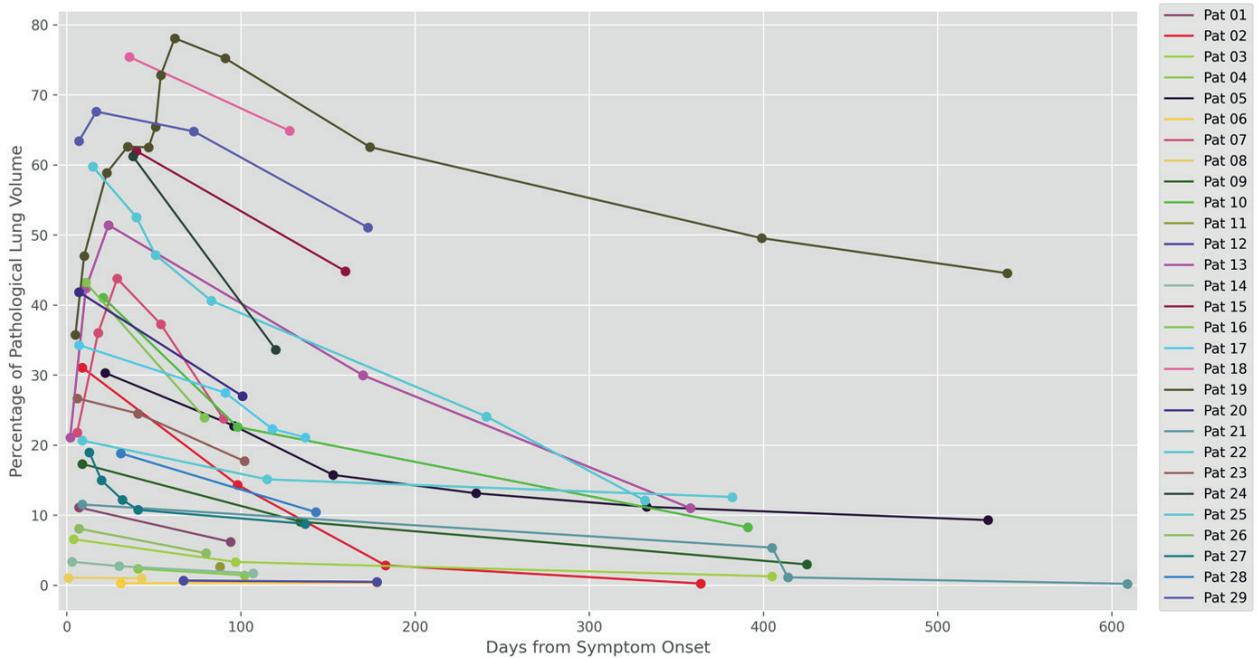
All of these abnormalities showed a lesser extent during follow-up. One single, focal lesion in each of 5 patients (5/157, 3 %) had appeared “de novo”. Table 3 outlines the transformations of findings over time.

### Results of objective image analysis

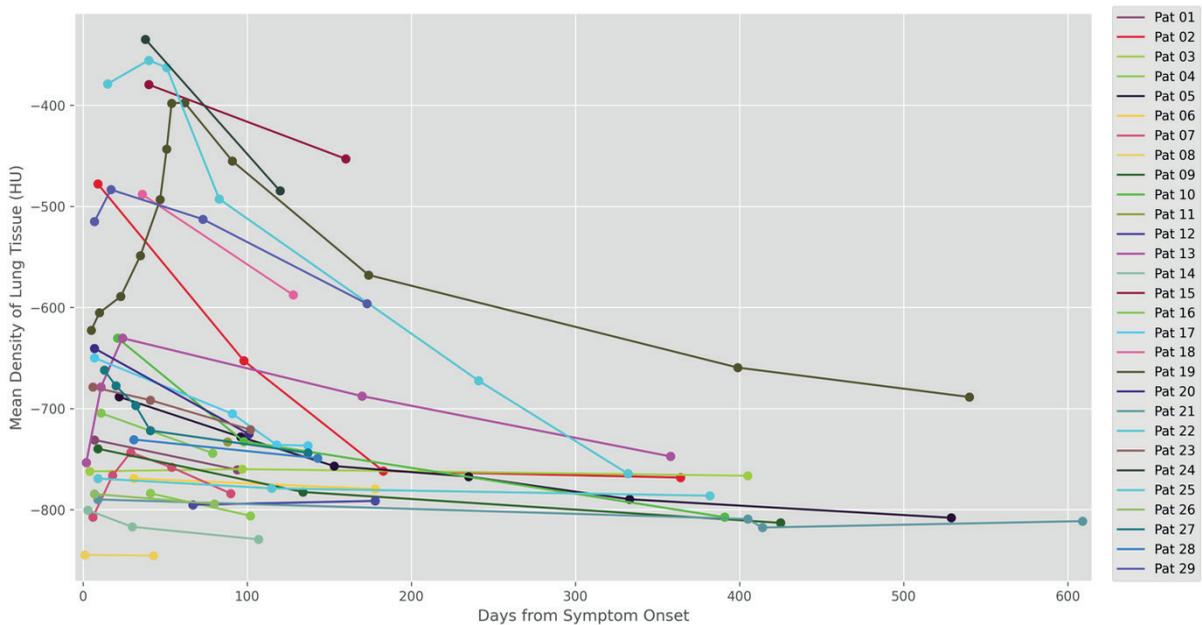
All consecutive chest CTs of the 29 patients acquired in the acute and chronic phase were analyzed regarding volume of pathological lung tissue (percentage) and lung tissue density (mean HU). Patient wise progressive graphs were established (figure 2). Both of the parameters showed a continuous decrease throughout the chronic phase in all of the 29 patients.



**Figure 2a:** Segmentation of pulmonary opacities in CTs throughout the course of disease. HRCT on day 20, 41 and 137 after symptom onset. Automatic segmentation of lung lesions using a pre-trained nnU-Net model. Pathologic lesions are marked in red. Stable localization and continuous decrease of volume of altered lung parenchyma is seen.



**Figure 2b.** Patient wise calculation of the percentage of opacified lung tissue. Each graph represents a patient, each point on the graph represents a scan. All graphs show a continuous decrease of volume of opacified lung tissue throughout the chronic phase.



**Figure 2c.** Patient wise calculation of mean lung tissue density. Each graph represents a patient, each time point on the graph represents a scan. All graphs show a continuous decrease of mean density of lung tissue throughout the chronic phase.

## Discussion

While acute COVID-19 is still a huge threat there is increasing data about debilitating long term sequelae referred to as “Long Covid” and “Post Covid”. Pathophysiology of Post Covid is not well understood. In particular, there is an ongoing debate if persistent lung abnormalities represent the residua after parenchymal injury caused by SARS-CoV 2 or if COVID-19 triggers a potentially progressive fibrotic “Post Covid-ILD” (31, 32). The optimal measure for clarification of this important issue would be lung biopsy which, however, is seldom performed due to its invasive nature. Several papers reported on the CT findings of patients recovering from COVID-19 (2, 4, 13, 14, 31, 33-36). However, all these reports suffer from a principal weakness in the study setups: The CT findings were merely reported as an average over all cases without acknowledging the intraindividual course of parenchymal lesions. However, from the radiological point of view mere evaluation of CT alterations at a given point in time is not suitable to distinguish post-infectious, possibly even fibrotic residua in terms of scarring from real, potentially progressive ILD because overlap is considerable. As for CT analysis, the only reasonable method for distinguishing post-infectious residua from ILD is the assessment of the evolution of parenchymal lesions over time intraindividually. This setup was called for in a widely noticed editorial before [32]. Parenchymal alterations which develop independently of the acute phase injury would favor the hypothesis of a self-contained ILD induced by SARS-CoV 2. Alterations in chronic phase CTs with a precursor in the acute phase which has decreased in volume and density over time suggest healing pneumonia with possibly end stage scarring/fibrotic-like lesions (the latter term is frequently used in literature to mark these lesions as possibly reversible as opposed to fixed fibrosis).

To the best of our knowledge this type of analysis has not been performed before. In order to fill this gap, our analysis of CT patterns focused on the regional linkage between single lesions on the CT scans of the acute phase and chronic period of the disease. The results support the hypothesis that the parenchymal abnormalities in the Post Covid phase do not represent an independent interstitial lung disease: First, the vast majority of abnormalities in

chronic phase CTs were preceded by lung injury at the very same location in the acute phase CT as opposed to de novo lesions. Particularly this applied to fibrotic-like lesions. Regional linkage of CT findings revealed that fibrotic-like lesions emerged from consolidation or GGO at the very same location in the acute phase (this is mirrored by the increasing number of reticulations and linear opacifications and simultaneously decreasing frequency of consolidation in the chronic phase, see table 2). This observation favors post-infectious injury over de novo ILD. Only one small, focal lesion in each of five patients had appeared de novo. But it has to be considered that the acute phase CT merely represented a snapshot of the entire course of disease. Thus, it cannot be ruled out that at some point in time later the respective lung zone might have been injured. Because in these five patients there were no CTs acquired in between the acute and chronic phase CT this could not be checked. Of note, we did not observe any new widespread fibrotic abnormalities in the chronic phase CTs.

Second, subjective and objective analysis of serial CTs demonstrated that abnormalities were stable in location and continuously decreasing in extent and density which is the expected finding in healing pneumonia. This also applied for the subset of patients with a follow-up of more than 170 days.

Third, the persisting abnormalities were predominantly GGO and linear opacities concordant with previous reports about healing COVID-19 pneumonia (2, 4, 12, 37). Of note, the same findings with a similar time course are seen in resolving pneumonia after SARS-CoV (38-40) and influenza (41-43) or after ARDS (42-46).

Currently there is still no consensus about imaging management in patients with Post Covid. In particular it is not clear which patient should be imaged at which time and with which modality. The British Thoracic Society issued a guidance in which performance of a CT (high-resolution CT and pulmonary embolism protocol) is recommended in patients who still have an abnormal chest X ray and/or pulmonary function test 12 weeks after discharge (47, 48). The European Society of Thoracic Imaging (ESTI) and the European Society of Radiology (ESR) recommend follow-up CT after 3 months (and 6 months in case of persistent lung abnormalities) in symptomatic patients who suffered from severe COVID-19 pneumonia or had

been hospitalized (49). Raghu et al. recommend a high-resolution baseline study without contrast, follow-up CT at 6 and 12 months as well as at 24 and 36 months, if fibrotic abnormalities persist (50). Basically, it seems to be reasonable to decide about imaging based on the patient's symptoms and lung function tests. This way lung abnormalities are not overseen but cost-effectiveness regarding both economic and radiation protection aspects are preserved.

During follow-up the above described "fibrotic-like" lesions could cause confusion in case no acute phase CT is available for comparison. They must not be uncritically interpreted as an fibrosing interstitial lung disease. In light of the results of the present study radiologists should rather bear in mind that these lesions may simply represent post-infectious scarring which may not resolve at all. Acknowledging this pitfall the ESTI/ERS recommend specific terms for the description of CT findings in Post Covid patients (49). In critical cases close follow-up will be needed to define their evolution and respiratory function tests will add some important information in order to distinguish between residua from potential progressive disease.

This study has limitations. The sample size was rather small. The cohort could unfortunately not be enlarged due to a change in the institutional standard operating procedure in March 2021 in so far that CTs for Post Covid patients were performed more restrictively. Moreover, the follow-up period was mean 134 days. Thus, our results have to be confirmed in long term studies. However, a subset of patients in our cohort was monitored for more than 170 days. The course of these patients' CT findings did not differ in any way from those with a shorter follow-up. According to hospital specific standard operating procedure the indication for a CT in the chronic phase was limited to patients with impaired lung function or worsening respiratory symptoms. Thus, the cohort represented a subset of patients with manifest pulmonary disease. Although formally a limitation we think that this bias does not hamper our results because detection of a potential Post Covid ILD would have been more likely in symptomatic than in asymptomatic patients. Correlation with histology was not possible because the clinical symptoms did not justify a biopsy.

## Conclusion

In summary, we evaluated the acute and chronic phase CTs of 29 patients with Post Covid syndrome. Regional intraindividual linkage revealed that findings on chronic phase CTs were preceded by lung injury in acute phase CTs. Moreover, subjective and objective analysis demonstrated that density and volume of parenchymal alterations decreased continuously during the study period. We conclude that long-term CT findings represent residua after acute pneumonia rather than Post Covid ILD. However, longer follow-up in larger cohorts is necessary to fully understand pathophysiology of Post Covid and to confirm our preliminary findings.

**List of abbreviations:** COVID-19: Corona Virus Disease 2019; SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus 2; MERS-CoV: Middle East Respiratory Syndrome; BGA: Blood gas analysis; PFT: Pulmonary Function Test; DLCO: Diffusion Capacity for Carbon Monoxide; MPR: Multiplanar Reformation; GGO: Ground Glass Opacity; ILD: Interstitial Lung Disease; ARDS: Acute Respiratory Distress Syndrome

**Funding:** This research was supported by the German Federal Ministry of Education and Research (BMBF) as part of the University Medicine Network (Project RACOON, 01KX2021).

**Conflicts of interest:** All authors declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

## References

1. Goërtz YMJ, Van Herck M, Delbressine JM, et al. Persistent symptoms 3 months after a SARS-CoV-2 infection: the post-COVID-19 syndrome? *ERJ Open Research*. 2020;6(4):00542-2020. doi: 10.1183/23120541.00542-2020.
2. Han X, Fan Y, Alwalid O, et al. Six-Month Follow-up Chest CT findings after Severe COVID-19 Pneumonia. *Radiology*. 2021;203153. doi: 10.1148/radiol.2021203153.
3. Shaw B, Daskareh M, Gholamrezanezhad A. The lingering manifestations of COVID-19 during and after convalescence: update on long-term pulmonary consequences of coronavirus disease 2019 (COVID-19). *Radiol Med*. 2021;126(1):40-6. doi: 10.1007/s11547-020-01295-8.
4. Sonnweber T, Sahanic S, Pizzini A, et al. Cardiopul-

- monary recovery after COVID-19 - an observational prospective multi-center trial. *Eur Respir J*. 2020. doi: 10.1183/13993003.03481-2020.
5. Mandal S, Barnett J, Brill SE, et al. 'Long-COVID': a cross-sectional study of persisting symptoms, biomarker and imaging abnormalities following hospitalisation for COVID-19. *Thorax*. 2020. doi: 10.1136/thoraxjnl-2020-215818.
  6. Truffaut L, Demey L, Bruyneel AV, et al. Post-discharge critical COVID-19 lung function related to severity of radiologic lung involvement at admission. *Respir Res*. 2021;22(1):29. doi: 10.1186/s12931-021-01625-y.
  7. Carfi A, Bernabei R, Landi F. Persistent Symptoms in Patients After Acute COVID-19. *Jama*. 2020;324(6):603-5. doi: 10.1001/jama.2020.12603.
  8. Halpin S, O'Connor R, Sivan M. Long COVID and chronic COVID syndromes. *J Med Virol*. 2021;93(3):1242-3. doi: 10.1002/jmv.26587.
  9. National Institute for Health and Care Excellence: Clinical Guidelines. COVID-19 rapid guideline: managing the long-term effects of COVID-19. National Institute for Health and Care Excellence: Clinical Guidelines. London: National Institute for Health and Care Excellence (UK) Copyright © NICE 2020.; 2020.
  10. Rabady S, Altenberger J, Brose M, et al. Leitlinie S1: Long COVID: Differenzialdiagnostik und Behandlungsstrategien. *Wiener klinische Wochenschrift*. 2021;133(7):237-78. doi: 10.1007/s00508-021-01974-0.
  11. Antoniou KM, Vasarmidi E, Russell AM, et al. European Respiratory Society Statement on Long COVID-19 Follow-Up. *Eur Respir J*. 2022. doi: 10.1183/13993003.02174-2021.
  12. Huang C, Huang L, Wang Y, et al. 6-month consequences of COVID-19 in patients discharged from hospital: a cohort study. *The Lancet*. 2021;397(10270):220-32. doi: 10.1016/s0140-6736(20)32656-8.
  13. Lee JH, Yim JJ, Park J. Pulmonary function and chest computed tomography abnormalities 6-12 months after recovery from COVID-19: a systematic review and meta-analysis. *Respir Res*. 2022;23(1):233. doi: 10.1186/s12931-022-02163-x.
  14. Li D, Liao X, Ma Z, et al. Clinical status of patients 1 year after hospital discharge following recovery from COVID-19: a prospective cohort study. *Ann Intensive Care*. 2022;12(1):64. doi: 10.1186/s13613-022-01034-4.
  15. Valenzuela C, Waterer G, Raghu G. Interstitial lung disease before and after COVID-19: a double threat? *Eur Respir J*. 2021;58(6). doi: 10.1183/13993003.01956-2021.
  16. Giacomelli C, Piccarducci R, Marchetti L, et al. Pulmonary fibrosis from molecular mechanisms to therapeutic interventions: lessons from post-COVID-19 patients. *Biochem Pharmacol*. 2021;193:114812. doi: 10.1016/j.bcp.2021.114812.
  17. Wild JM, Porter JC, Molyneux PL, et al. Understanding the burden of interstitial lung disease post-COVID-19: the UK Interstitial Lung Disease-Long COVID Study (UKILD-Long COVID). *BMJ Open Respir Res*. 2021;8(1). doi: 10.1136/bmjresp-2021-001049.
  18. Udwadia ZF, Koul PA, Richeldi L. Post-COVID lung fibrosis: The tsunami that will follow the earthquake. *Lung India*. 2021;38(Supplement):S41-s7. doi: 10.4103/lungindia.lungindia\_818\_20.
  19. Wijsenbeek M, Cottin V. Spectrum of Fibrotic Lung Diseases. *N Engl J Med*. 2020;383(10):958-68. doi: 10.1056/NEJMra2005230.
  20. Ackermann M, Verleden SE, Kuehnel M, et al. Pulmonary Vascular Endothelialitis, Thrombosis, and Angiogenesis in Covid-19. *New England Journal of Medicine*. 2020;383(2):120-8. doi: 10.1056/NEJMoa2015432.
  21. Ciaffi J, Meliconi R, Ruscitti P, et al. Rheumatic manifestations of COVID-19: a systematic review and meta-analysis. *BMC Rheumatol*. 2020;4:65. doi: 10.1186/s41927-020-00165-0.
  22. Paliwal VK, Garg RK, Gupta A, et al. Neuromuscular presentations in patients with COVID-19. *Neurol Sci*. 2020;41(11):3039-56. doi: 10.1007/s10072-020-04708-8.
  23. Bonometti R, Sacchi MC, Stobbione P, et al. The first case of systemic lupus erythematosus (SLE) triggered by COVID-19 infection. *Eur Rev Med Pharmacol Sci*. 2020;24(18):9695-7. doi: 10.26355/eurev\_202009\_23060.
  24. Gooding R, Myers B, Salta S. Lupus Anticoagulant in Patients with Covid-19. *N Engl J Med*. 2020;383(19):1893. doi: 10.1056/NEJMc2027508.
  25. Zhang Y, Xiao M, Zhang S, et al. Coagulopathy and Antiphospholipid Antibodies in Patients with Covid-19. *N Engl J Med*. 2020;382(17):e38. doi: 10.1056/NEJMc2007575.
  26. Hansell DM, Bankier AA, MacMahon H, et al. Fleischner Society: glossary of terms for thoracic imaging. *Radiology*. 2008;246(3):697-722. doi: 10.1148/radiol.2462070712.
  27. Hofmanninger J, Prayer F, Pan J, et al. Automatic lung segmentation in routine imaging is primarily a data diversity problem, not a methodology problem. *Eur Radiol Exp*. 2020;4(1):50. doi: 10.1186/s41747-020-00173-2.
  28. Isensee F, Jaeger PF, Kohl SAA, et al. nnU-Net: a self-configuring method for deep learning-based biomedical image segmentation. *Nat Methods*. 2021;18(2):203-11. doi: 10.1038/s41592-020-01008-z.
  29. Roth H, Xu Z, Diez CT, et al. Rapid Artificial Intelligence Solutions in a Pandemic - The COVID-19-20 Lung CT Lesion Segmentation Challenge. *Res Sq*. 2021. doi: 10.21203/rs.3.rs-571332/v1.
  30. Yushkevich PA, Piven J, Hazlett HC, et al. User-guided 3D active contour segmentation of anatomical structures: significantly improved efficiency and reliability. *Neuroimage*. 2006;31(3):1116-28. doi: 10.1016/j.neuroimage.2006.01.015.
  31. Myall KJ, Mukherjee B, Castanheira AM, et al. Persistent Post-COVID-19 Inflammatory Interstitial Lung Disease: An Observational Study of Corticosteroid Treatment. *Annals of the American Thoracic Society*. 0(ja):null. doi: 10.1513/AnnalsATS.202008-1002OC.
  32. Wells AU, Devaraj A, Desai SR. Interstitial Lung Disease after COVID-19 Infection: A Catalog of Uncertain-

- ties. *Radiology*. 2021;299(1):E216-E8. doi: 10.1148/radiol.2021204482.
33. Marvisi M, Ferrozzi F, Balzarini L, et al. First report on clinical and radiological features of COVID-19 pneumonia in a Caucasian population: Factors predicting fibrotic evolution. *Int J Infect Dis*. 2020;99:485-8. doi: 10.1016/j.ijid.2020.08.054.
34. Lerum TV, Aaløkken TM, Brønstad E, et al. Dyspnoea, lung function and CT findings 3 months after hospital admission for COVID-19. *Eur Respir J*. 2021;57(4). doi: 10.1183/13993003.03448-2020.
35. Wu X, Liu X, Zhou Y, et al. 3-month, 6-month, 9-month, and 12-month respiratory outcomes in patients following COVID-19-related hospitalisation: a prospective study. *Lancet Respir Med*. 2021;9(7):747-54. doi: 10.1016/s2213-2600(21)00174-0.
36. Bocchino M, Lieto R, Romano F, et al. Chest CT-based Assessment of 1-year Outcomes after Moderate COVID-19 Pneumonia. *Radiology*. 2022;305(2):479-85. doi: 10.1148/radiol.220019.
37. Guan CS, Lv ZB, Li JJ, et al. CT appearances, patterns of progression, and follow-up of COVID-19: evaluation on thin-section CT. *Insights Imaging*. 2021;12(1):73. doi: 10.1186/s13244-021-01019-0.
38. Chang YC, Yu CJ, Chang SC, et al. Pulmonary sequelae in convalescent patients after severe acute respiratory syndrome: evaluation with thin-section CT. *Radiology*. 2005;236(3):1067-75. doi: 10.1148/radiol.2363040958.
39. Ng CK, Chan JW, Kwan TL, et al. Six month radiological and physiological outcomes in severe acute respiratory syndrome (SARS) survivors. *Thorax*. 2004;59(10):889-91. doi: 10.1136/thx.2004.023762.
40. Hui DS, Wong KT, Ko FW, et al. The 1-year impact of severe acute respiratory syndrome on pulmonary function, exercise capacity, and quality of life in a cohort of survivors. *Chest*. 2005;128(4):2247-61. doi: 10.1378/chest.128.4.2247.
41. Qiao J, Zhang M, Bi J, et al. Pulmonary fibrosis induced by H5N1 viral infection in mice. *Respir Res*. 2009;10(1):107. doi: 10.1186/1465-9921-10-107.
42. Chen J, Wu J, Hao S, et al. Long term outcomes in survivors of epidemic Influenza A (H7N9) virus infection. *Sci Rep*. 2017;7(1):17275. doi: 10.1038/s41598-017-17497-6.
43. Bai L, Gu L, Cao B, et al. Clinical features of pneumonia caused by 2009 influenza A(H1N1) virus in Beijing, China. *Chest*. 2011;139(5):1156-64. doi: 10.1378/chest.10-1036.
44. Desai SR, Wells AU, Rubens MB, et al. Acute respiratory distress syndrome: CT abnormalities at long-term follow-up. *Radiology*. 1999;210(1):29-35. doi: 10.1148/radiology.210.1.r99ja2629.
45. Burnham EL, Janssen WJ, Riches DW, et al. The fibroproliferative response in acute respiratory distress syndrome: mechanisms and clinical significance. *Eur Respir J*. 2014;43(1):276-85. doi: 10.1183/09031936.00196412.
46. Zompatori M, Ciccarese F, Fasano L. Overview of current lung imaging in acute respiratory distress syndrome. *Eur Respir Rev*. 2014;23(134):519-30. doi: 10.1183/09059180.00001314.
47. Peter MG, Shaney LB, Robin C, et al. Respiratory follow-up of patients with COVID-19 pneumonia. *Thorax*. 2020;75(11):1009. doi: 10.1136/thoraxjnl-2020-215314.
48. Society BT: British Thoracic Society guidance on respiratory follow up of patients with a clinico-radiological diagnosis of COVID-19 pneumonia. <https://www.brit-thoracic.org.uk/covid-19/covid-19-information-for-the-respiratory-community/> (2020). Accessed 11.06.2023.
49. Martini K, Larici AR, Revel MP, et al. COVID-19 pneumonia imaging follow-up: when and how? A proposition from ESTI and ESR. *Eur Radiol*. 2022;32(4):2639-49. doi: 10.1007/s00330-021-08317-7.
50. Raghu G, Wilson KC. COVID-19 interstitial pneumonia: monitoring the clinical course in survivors. *The Lancet Respiratory Medicine*. 2020;8(9):839-42. doi: [https://doi.org/10.1016/S2213-2600\(20\)30349-0](https://doi.org/10.1016/S2213-2600(20)30349-0).