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Quantitative image analysis in COVID-19 acute respiratory distress syndrome: a cohort observational study.

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Publication Date

2021

DOI

10.12688/f1000research.75311.2

Peer reviewed



RESEARCH ARTICLE

REVISED Quantitative image analysis in COVID-19 acute respiratory distress syndrome: a cohort observational study.
[version 3; peer review: 2 approved]

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V3 First published: 09 Dec 2021, 10:1266
<https://doi.org/10.12688/f1000research.75311.1>
Second version: 24 May 2022, 10:1266
<https://doi.org/10.12688/f1000research.75311.2>
Latest published: 31 Mar 2023, 10:1266
<https://doi.org/10.12688/f1000research.75311.3>

Abstract**Background**

Acute respiratory distress syndrome (ARDS) is a severe form of acute lung injury commonly associated with pneumonia, including coronavirus disease-19 (COVID-19). The resultant effect can be persistent lung damage, but its extent is not known. We used quantitative high resolution computed tomography (QHR-CT) lung scans to radiographically characterize the lung damage in COVID-19 ARDS (CARDS) survivors.

Methods

Patients with CARDS (N=20) underwent QHR-CT lung scans 60 to 90 days after initial diagnosis, while hospitalized at a long-term acute care hospital (LTACH). QHR-CT assessed for mixed disease (QMD), ground glass opacities (QGGO), consolidation (QCON) and normal lung tissue (QNL). QMD was correlated with respiratory support on admission, tracheostomy decannulation and supplementary oxygen need on discharge.

Results

Sixteen patients arrived with tracheostomy requiring invasive mechanical ventilation. Four patients arrived on nasal oxygen support. Of the patients included in this study 10 had the tracheostomy cannula removed, four remained on invasive ventilation, and two died. QHR-CT showed 45% QMD, 28.1% QGGO, 3.0% QCON and QNL=23.9%. Patients with mandatory mechanical ventilation had the highest proportion of QMD when compared to no mechanical ventilation. There was no correlation between QMD and tracheostomy decannulation or need for supplementary oxygen at discharge.

Open Peer Review

Approval Status

	1	2
version 3 (revision) 31 Mar 2023		 view
version 2 (revision) 24 May 2022		 view
version 1 09 Dec 2021	 view	

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Any reports and responses or comments on the article can be found at the end of the article.

Conclusions

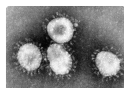
Our data shows severe ongoing lung injury in patients with CARDS, beyond what is usually expected in ARDS. In this severely ill population, the extent of mixed disease correlates with mechanical ventilation, signaling formation of interstitial lung disease. QHR-CT analysis can be useful in the post-acute setting to evaluate for interstitial changes in ARDS.

Keywords

acute respiratory distress syndrome, COVID-19, quantitative high-resolution lung CT scanning



This article is included in the **Emerging Diseases and Outbreaks** gateway.



This article is included in the **Coronavirus** collection.

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Competing interests: No competing interests were disclosed.

Grant information: The author(s) declared that no grants were involved in supporting this work.

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How to cite this article: Dolinay T, Jun D, Maller A *et al.* **Quantitative image analysis in COVID-19 acute respiratory distress syndrome: a cohort observational study.** [version 3; peer review: 2 approved] F1000Research 2023, 10:1266 <https://doi.org/10.12688/f1000research.75311.3>

First published: 09 Dec 2021, 10:1266 <https://doi.org/10.12688/f1000research.75311.1>

REVISED Amendments from Version 2

Based on the reviewers recommendation, we corrected in the Methods section to address that all study patients required positive pressure mechanical ventilation with at least 5 cm H₂O end expiratory pressure prior to the enrolment. We also added a new reference to the Discussion section to discuss continued imaging surveillance post ARDS.

Any further responses from the reviewers can be found at the end of the article

Introduction

Acute respiratory distress syndrome (ARDS) is a severe form of lung injury requiring intensive care unit (ICU) hospitalization. The etiology of ARDS is broad, but approximately 40% of cases are complications of respiratory infections¹. Despite modern intensive care the mortality of ARDS remains above 30%^{2,3} and international statistics show that ARDS is responsible for approximately 10% of all ICU admissions³. During the 2020–2021 coronavirus disease (COVID)-19 pandemic, ARDS emerged as a feared complication of COVID-19 pneumonia driving ICU hospitalizations and mortality^{4,5}. Clinical data also suggest that recovery from COVID-19-associated ARDS (CARDS) is prolonged requiring ongoing respiratory support beyond what is traditionally seen in ICU care^{6,7}.

High resolution-computer tomography (HR-CT) scans with quantitative analysis (QHR-CT) have been widely used to study the details of the lung parenchyma^{8,9} and have been beneficial in tracking the progression of interstitial lung disease¹⁰. In ARDS, the use of CT analysis was initially hindered by concerns over transportation of the critically ill. However with portable and faster CT scanners available in routine clinical care, HR-CTs have proved its usefulness in determining alveolar damage and edema formation^{11,12}. Less is known regarding its utility in following the clinical course of the disease as lung infiltrates seen in the acute phase of ARDS usually resolve¹³. In spite of this, in a minority of patients, pulmonary fibrosis may develop which has been associated with poor outcome¹⁴. Recently McGroder *et al.* and in a separate analysis Gonzalez *et al.* reported persistent lung infiltrates and fibrosis-like changes 3–4 months after severe COVID pneumonia^{6,7}. This may suggest that persistent lung changes in ARDS are more common than initially reported.

In our study, we examined the extent of persistent lung changes in CARDS survivors requiring continued hospitalization. Our findings suggest ongoing lung damage, which may give rise to pulmonary fibrosis.

Methods**Patient enrollment**

Our study was approved by the Western Institutional Review Board (IRB) protocol ID #20210635. In this single center observational cohort study, patients admitted to Barlow Respiratory Hospital (BRH) with a diagnosis of CARDS

were considered for enrollment. To avoid selection bias, we approached consecutively admitted patients to participate in the study. BRH is a non-profit long-term acute care hospital (LTACH) serving the greater Los Angeles area. Patients are transferred to BRH for ongoing respiratory care from short-term acute care hospitals (STACH). CARDS diagnosis was made during STACH hospitalization based on the following criteria: 1. at least one positive COVID-19 PCR test on admission to STACH, 2. new bilateral lung infiltrates in the past seven days on chest imaging not attributed to pulmonary edema alone, 3. requirement for invasive or non-invasive mechanical ventilation with at least 5 cm H₂O positive end-expiratory pressure, 4. ratio of partial arterial oxygen pressure (PaO₂) and fraction of inspired oxygen (FiO₂) <300. All patients required positive pressure mechanical ventilation prior to the enrollment in the study.

To participate in the study, informed written consent was obtained directly from the patient by the investigators. In case, the patient was not directly consentable, per the IRB recommendations, consent was obtained from the patient's power of attorney. We enrolled 25 patients in our study between February and July 2021. Patients were consented to undergo lung QHR-CT during BRH admission. From the 25 enrolled patients, 20 completed the CT scans and their demographic and clinical data was collected by chart review. Data was entered in a password protected database. We did not record data of the patients, who did not complete the CT scans to avoid bias from an incomplete dataset.

The original QHR-CT scans and database contain sensitive patient information and is not publicly available for review per IRB guidelines. We created a deidentified database to share with the readers, which contains all pertinent patient demographics, clinical data, QHR-CT scan scores and volume measurements. This database is uploaded in a public database¹⁵.

Demographics and clinical data

Patients' age, gender, race, ethnicity, STACH admission date, LTACH admission date, CT scan date, premorbid medical condition, tracheostomy status on admission, presence or absence of mechanical ventilation and mechanical ventilation mode were collected at the time of LTACH admission. The following premorbid conditions were considered: bacterial pneumonia, pneumothorax, acute or chronic kidney disease, hypertension, diabetes mellitus, deep vein thrombosis (DVT), pulmonary embolism (PE), heart failure, coronary artery disease (CAD), cerebrovascular accident (CVA), obesity with body mass index greater than 30 and pulmonary fibrosis. During LTACH stay data was collected for inpatient death, need for continued mechanical ventilation, on tracheostomy decannulation status and fraction of inspired oxygen (FiO₂) on discharge.

Image analysis

HR-CT lung scans were performed using a General Electric BrightSpeed 16 slice CT scanner (Model # 5128609-2, General

Electric Health Corporation, Chicago, IL, USA) with 2mm cuts at BRH. QHR-CT analysis was performed by University of California Los Angeles (UCLA) Radiology department. Quantitative scores were measures for four distinct radiological patterns: 1. ground glass opacity, (QGGO), 2. mixed diseases (QMD), 3. consolidation (QCON) and 4. normal lung (QNL). The sum of three abnormal lung tissue scores was named the quantitative total lung diseases (QTLD). We applied the domain adaptation for calculating quantitative COVID-19 scores from HR-CT images. Quantitative lung scores were expressed as percent of predicted total lung capacity (% of TLC) calculated from HR-CT. To calculate the % of TLC, we used the formula $(TLC \text{ volume from HR-CT}) / ((7.99 * \text{height}) - 7.08) * 100$ for men and $(TLC \text{ volume from HR-CT}) / ((6.6 * \text{height}) - 5.79) * 100$ for women. The source data and technique were adapted from the previously developed algorithm for diffuse lung disease^{16,17} and the target data was HR-CT images containing consolidation¹⁸. The final model was reviewed and visually confirmed using an independent COVID-19 cohort at UCLA. Ground glass opacities usually represent acute inflammatory processes, mixed disease is commonly a radiological presentation of interstitial lung disease (ILD) and consolidation is frequently associated with pulmonary infection¹⁹.

Mechanical ventilation

Based on the need for mechanical ventilation at LTACH admission, three groups of patients were created: 1. mandatory mode mechanical ventilation via tracheostomy (MV), 2. spontaneous mode mechanical ventilation via tracheostomy (SV) and no need for mechanical ventilation (NV). MV included volume control ventilation, pressure control ventilation, and synchronized intermittent mandatory ventilation. SV included pressure support ventilation.

Statistics

Patient characteristics and mechanical ventilation data were expressed as a percentage of total. Age and FiO₂ were expressed as mean± standard deviation (SD). The lung disease score was expressed as % of TLC± interquartile range (IQR). The extent of mixed disease (QMD) was expressed as QMD/TLC± IQR and QMD/QTLD± IQR. QMD was correlated with the presence of mechanical ventilation on admission, tracheostomy decannulation. Statistical analysis was performed using non-parametric Kruskal-Wallis equality-of-population rank test with Bonferroni correction for the multiple comparisons. p < 0.05 was considered statistically significant. Correlation coefficient was calculated between the discharge FiO₂, QMD and QMD/QTLD and data is shown with 95% confidence interval (95%CI). Stata 14.1 software (College Station, Texas 77845 USA, RRID:SCR_012763) was used for statistical analysis.

Results

Patient characteristics

We analyzed the CT images of 8 female and 12 male patients. The mean age was 61.2 years. There were 2 Asian, 1 American Indian/Native Alaskan, 3 African American, 6 Latino and 8 White patients in our cohort. Twelve patients were

Non-Hispanic and 8 patients were Hispanic. At the time of LTACH admission 16 patients had tracheostomy and required invasive mechanical ventilation, 2 patients arrived on high flow oxygen support and 2 patients needed low flow oxygen. Of the 20 patients, 16 patients had secondary bacterial, 7 patients had pneumothorax secondary to mechanical ventilation, 9 patients had renal disease, 12 had hypertension, 12 had diabetes mellitus, 6 had DVT, 2 had PE, 3 patients suffered from heart disease, 3 had recent CVA, 9 were obese and none of the patients had a prior diagnosis of pulmonary fibrosis. Demographics and premorbid conditions are shown in **Table 1**.

Respiratory support

Specifics of airway management, mechanical ventilation and liberation from mechanical ventilation are listed in **Table 2**

Table 1. Patient demographics and premorbid conditions on LTACH arrival.

Characteristic	N = 20
Gender, Female N (%)	8 (40.0)
Age, Mean (SD)	62.1 (10.3)
Race, N (%)	
American Indian/Native Alaskan	1 (5.0)
Asian	2 (10.0)
Black/African American	3 (15.0)
Hispanic/Latino	6 (30.0)
White	8 (40.0)
Ethnicity, N (%)	
Hispanic	8 (40.0)
Non-Hispanic	12 (60.0)
Premorbid condition	
Bacterial pneumonia N (%)	16 (80)
Pneumothorax N (%)	7 (35)
Kidney disease N (%)	9 (45)
Hypertension N (%)	12 (60)
Diabetes mellitus N (%)	12 (60)
DVT N (%)	6 (30)
PE N (%)	2 (10)
Heart failure N (%)	3 (15)
CAD N (%)	2 (10)
CVA N (%)	3 (15)
Obesity N (%)	9 (45)
Pulmonary fibrosis N (%)	0 (0)

Table 2. Respiratory support in CARDS patients.

	N = 20
Respiratory support on admission	
VC N (%)	10 (50)
PCV N (%)	3 (15)
PS N (%)	3 (15)
High flow nasal cannula N (%)	2 (10)
Low flow nasal cannula N (%)	2 (10)
Tracheostomy N (%)	16 (80)
Respiratory support on discharge	
Decannulated N (%)	10 (50)
VC N (%)	2 (10)
Low flow nasal cannula N (%)	13 (65)
No respiratory support N (%)	5 (25)
FiO ₂ % Mean (SD)	27.2 (6.8)
Inpatient mortality N (%)	2 (10)

and can also be found in the online database. Sixteen patients required invasive mechanical ventilation via tracheostomy on LTACH admission. Of those 13 arrived with MV and 3 with SV. Four patients needed supplementary oxygen via nasal cannula, 2 with high flow and 2 with low flow (less than 10 liters per minute) systems. Twelve patients were liberated from mechanical ventilation and 10 patients had the tracheostomy cannula removed (decannulated) before LTACH discharge. Two patients needed continued MV on discharge. Two patients died during the LTACH stay. No patients required resumption of mechanical ventilation. Five patients were discharged on room air. The average supplementary FiO₂ on discharge was 27.6% (SD = 6.8).

Quantitative lung injury scores correlate with disease severity on admission

QHR-CT was performed between two and three months post diagnosis of CARDS. The average predicted TLC was low, 2175.3 ml (SD=574.1), mean % of TLC=38.48 (SD=13.9). There was significant persistent lung damage with QTLD = 76.1% (IQR=15.6) of TLC. The majority of lung pathology was QMD with 45.0% (IQR=24.7) of TLC. QGGO was 28.1% (IQR=9.6), QCON was 3.0% (IQR=4.5) with little normal lung tissue remaining QNL = 23.9% (IQR=15.6). The distribution of lung disease was equal in both lungs (data not shown). Table 3 shows the extent of lung disease in relation to TLC. Figure 1A shows an example of the distribution of lung disease on CT scan and Figure 1B depicts the patterns of lung abnormalities in color coded fashion.

Table 3. Quantitative HR-CT scores by pattern in CARDS.

QHRCT score	% of TLC (IQR)
QGGO	28.1 (9.6)
QMD	45.0 (24.7)
QCON	3.0 (4.5)
QTLD	76.1 (15.6)
QNL	23.9 (15.6)

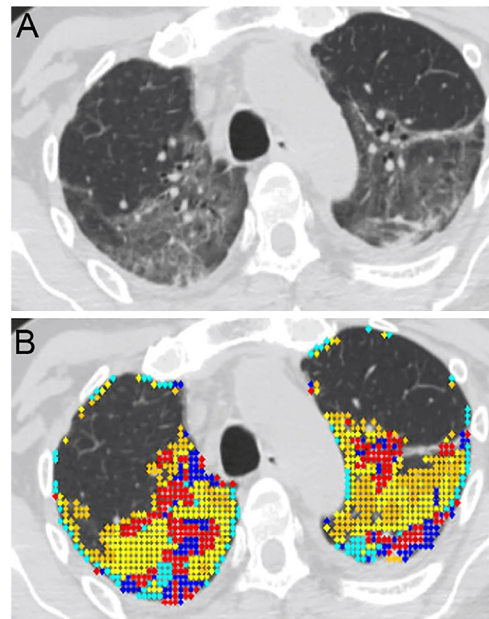


Figure 1. Quantitative high-resolution CT analysis of COVID-19 acute respiratory distress syndrome (ARDS). A. Horizontal high resolution (HR)-CT lung cut of a selected COVID-19 ARDS (CARDS) patient. The patient is a 61-year-old male with mandatory mechanical ventilation on arrival to the long-term-acute care facility. B. Color coded quantitative HR-CT (QHR-CT) analysis in CARDS. Quantitative scores were 19.1% mixed disease (QMD), 25.1% of ground glass opacities (QGGO) and 3.4% consolidation (QCON). The ratio of QMD to quantitative total lung diseases (QTLD) was 40.1%. Red and blue = mixed disease (QMD), yellow and cyan = ground glass opacities (QGGO), peach = consolidation (QCON).

The extent of QMD was correlated with admission use of respiratory support (Table 4). Patients with MV and SV had more QMD than their NV counterparts. When QMD/QTLD ratio was calculated, MV patients had significantly higher ratio than NV patients (p < 0.0127). There was no correlation between the extent of QMD and tracheostomy decannulation or need for supplementary oxygen on discharge (Table 4).

Table 4. The relationship between quantitative mixed disease score and respiratory support on LTACH admission and discharge.

	QMD scores (% of TLC), mean (IQR)	QMD/QTLD, mean (IQR)
Respiratory support on admission		
MV (N = 13)	50.4 (17.9)	0.6 (0.1)
SV (N = 3)	41.4 (40.4)	0.5 (0.3)
NV (N = 4)	30.3 (10.5)	0.4 (0.1)*
Tracheostomy decannulated before discharge		
Yes	48.4 (17.9)	0.6 (0.1)
No	49.2 (24.4)	0.6 (0.2)
Use of supplementary FiO ₂ on discharge	QMD scores (% of TLC), Correlation Coefficient (95% CI)	QMD/QTLD, Correlation Coefficient (95% CI)
Yes	0.264 (−0.231 – 0.651)	0.327 (−0.165 – 0.689)

* Represents significant difference between MV and NV, $p = 0.0127$, Kruskal-Wallis test; IQR=interquartile range

Discussion

Modern ICU care significantly improved the immediate survival of ARDS, but little is known about the long-term respiratory complications of the disease^{3,20}. Herridge *et al.* reported that 20% of ARDS survivors have abnormal chest imaging at one year²¹ and more recently Burnham *et al.* showed that 25% ARDS survivors may have ILD at six months²². The etiology of persistent interstitial lung changes post ARDS is not well understood, but it has been associated with poor quality of life^{14,22}. During the COVID-19 pandemic, ARDS cases soared⁵ and preliminary studies suggest that 30-40% of critically ill COVID-19 patients have persistent lung changes^{6,7}. It has been long speculated that a major factor for the development in ILD in ARDS is invasive positive pressure mechanical ventilation (commonly abbreviated mechanical ventilation)²³. Although lifesaving, mechanical ventilation has been associated with increased rates of pulmonary fibrosis post ARDS¹⁴. Recently McGroder *et al.* showed fibrosis-like radiographic changes in 72% patients receiving mechanical ventilation compared to 20% of non-ventilated COVID-19 patients⁶. The etiology of fibrosis is unclear but our imaging analysis in agreement with other studies that describe a non-specific post-inflammatory origin^{7,14}. All together this data suggests that survivors of CARDS maybe prone to ILD and pulmonary fibrosis thus, requiring long-term monitoring²⁴.

In our study we performed QHR-CT lung analysis of CARDS survivors, who require ongoing respiratory care two to three months after the initial diagnosis. LTACH patients represent a unique population of the chronically critically ill with significant morbidity and mortality. We have previously reported that 80% of COVID-19 patients requiring LTACH admission have tracheostomy and 51% are receiving mechanical ventilation²⁵. In this severely ill population, it is difficult to apply lung function testing and quality of life questionnaires to assess respiratory status. QHR-CT has been useful in following patients with ILD and can detect disease progression¹⁰. HR-CT can be relatively easily performed in non-cooperative patients

and quantitative analysis provides insight to the ongoing lung disease. We found that in our population of CARDS patients, there was significant lung disease involving, on average, 76% of the lungs. The most significant form of lung changes (45%) were consistent with mixed disease, which is a combination of reticulation and traction bronchiectasis, suggesting ILD. ILD changes usually result in permanent scarring and can lead to pulmonary fibrosis. In comparison, ground glass opacities and consolidation seen with acute inflammation and infections usually resolve. These findings suggest that ILD is more common in CARDS than other forms of ARDS. We also observed that patients who did not require mechanical ventilation on admission, had less ILD, which is consistent with findings of McGroder *et al.*⁶ However, we did not find association between the extent of mixed disease and tracheostomy decannulation or need for supplementary oxygen at discharge. This data signals that the cessation of mechanical ventilation or lower oxygen supplementation will not reverse the damage that has already occurred. In concert with our findings, in a recent meta-analysis, Wanatabe *et al.* found that lung changes are common 1-year post CARDS and recommended continued imaging surveillance to ensure resolution²⁶.

Our study has several strengths: 1. it studies a chronically critically ill population, in which the outcomes of ARDS are not known, 2. it shows that QHR-CT can be easily used to study lung disease in a population where traditional respiratory tests are difficult to perform, 3. it adds to our understanding of ILD development post ARDS. However, our study also has limitations: 1. it studies a small group of CARDS patients in a single hospital in Los Angeles, California, which may limit generalizability; 2. CARDS is a complex disease and our limited dataset allowed only the analysis of a select number of respiratory parameters, which may not have taken into account other possible confounders in our analysis; 3. QHR-CT technology is not specific to ARDS and some of the unique pathologic and radiographic changes of this disease may have been missed; 4. we did not perform serial imaging and we do

not know, if the observed mixed disease, will progress with time; 5. lastly, we used HR-CT technology which results in radiation exposure.

Conclusions

In conclusion, our study suggests that lung disease is highly prevalent in CARDS two to three months after the initial infection. ILD is the most prominent findings on imaging, which may result in progression to fibrotic disease. We recommend following CARDS patients with HR-CT beyond the acute care setting to evaluate for the development of ILD.

Consent statement

Informed written consent was obtained directly from the patient by the investigators. In case, the patient was not

directly contactable, per the IRB recommendations, consent was obtained from the patient's power of attorney.

Data availability

Underlying data

OSF: CT in COVID <https://doi.org/10.17605/OSF.IO/S2FXN>¹⁵.

The project contains the following underlying data:

- CT database-deidentified_final_with_CT_scores_11-18-21.xlsx

Data are available under the terms of the [Creative Commons Zero "No rights reserved" data waiver](#) (CC0 1.0 Public domain dedication).

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Version 3

Reviewer Report 12 May 2023

<https://doi.org/10.5256/f1000research.146057.r168408>

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Prashant Nasa 

Head Critical Care Medicine, NMC Specialty Hospital, Dubai, United Arab Emirates

I agree with the reply comments by the authors and do not have any new comments.

Competing Interests: No competing interests were disclosed.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Version 2

Reviewer Report 20 March 2023

<https://doi.org/10.5256/f1000research.134257.r164894>

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Prashant Nasa 

Head Critical Care Medicine, NMC Specialty Hospital, Dubai, United Arab Emirates

I was privileged to review a manuscript on quantitative image analysis in COVID-19 related ARDS cohort observational study.

The manuscript is very well written, and the research topic is engaging. The major limitation of this study is its small size, which should be acknowledged in the conclusion and abstract. The results from this study must be validated in a prospective larger cohort.

There are minor concerns.

1. In the criteria for diagnosis of CARDS, the second criteria mention the use of at least 5 cm of H₂O positive pressures. Instead, it should be corrected to at least 5 cm of H₂O positive end-expiratory pressure.
2. 4 out of 20 patients were on low or high-flow oxygen. These patients cannot be classified into ARDS criteria. Were these patients needed ventilatory support in the short-term acute care facility?
3. The CT findings of mixed disease in the discussion suggest progression to interstitial lung disease. Isolated findings alone cannot be used for the diagnosis of interstitial lung disease in these patients. Many of these radiographic findings entirely resolved over a duration¹. Close monitoring is advocated with imaging is advocated to evaluate the progression or persistence of these findings.

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Is the work clearly and accurately presented and does it cite the current literature?

Yes

Is the study design appropriate and is the work technically sound?

Yes

Are sufficient details of methods and analysis provided to allow replication by others?

Yes

If applicable, is the statistical analysis and its interpretation appropriate?

Yes

Are all the source data underlying the results available to ensure full reproducibility?

Yes

Are the conclusions drawn adequately supported by the results?

Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: COVID-19 related ARDS

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 23 Mar 2023

Tamas Dolinay

We would like to thank the reviewer for the useful comments. Please see below our point-by-point response:

1. In the revised manuscript, we corrected the definition of ARDS and added 5 cmH2O positive end-expiratory pressure.
2. We amended our Patients enrollment description to include that all patients had met ARDS diagnosis criteria prior to study enrollment, which included positive pressure ventilation.
3. Thank you for this important question. We agree with the reviewer that the frequency pulmonary fibrosis and interstitial lung disease (ILD) post-ARDS are not known and further research is needed to study these questions. The lack of data is likely related to the facts that 1) there are multiple disease mechanisms resulting in ARDS and 2) there is no definition for post-ARDS chronic lung disease. Chronic lung changes are commonly described in COVID-19-associated ARDS (CARDS), as pointed out in the reference provided, and a growing body of literature suggests that the resolution of interstitial lung changes maybe slower in CARDS than in other forms of ARDS. We agree with Watanabe and colleagues that “fibrotic-like changes” that can be seen in CARDS are not equal to “COVID-related fibrosis”, but can be recognized as risk factor for development of fibrosis. However the mixed disease, marked by reticulation and traction bronchiectasis on qualitative- high resolution CT scanning (QHR-CT) show the image findings of ILD. This does not equal to permanent lung fibrosis but can be a sign of the development of permanent lung scarring. We believe our findings are in concert with theirs and our publication adds to the literature that supports continued monitoring of patients post CARDS. We added the reference to the revised version of the manuscript.

Competing Interests: No competing interests were disclosed.

Version 1

Reviewer Report 03 May 2022

<https://doi.org/10.5256/f1000research.79165.r135370>

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Jeffrey Haspel

Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, Washington

University School of Medicine, St. Louis, MO, USA

Here, Dolinay and colleagues report the prevalence of radiographic abnormalities in a cohort of COVID-19 survivors admitted to their LTACH. They note a high prevalence of CT abnormalities 2-3 months post COVID, consistent with ILD, and based on this suggest the need for long term radiographic follow up.

Overall, this is an interesting report that, combined with reports sure to follow from other centers, will be useful in clarifying the natural history of severe COVID-19.

My comments are minor:

1. Since TLC is reported as "low" based on CT, it would be helpful to supply the %predicted TLC.
2. Since the use of Kruskal Wallis suggests the data presented are non-parametric it is probably more correct to report IQR rather than SD/SE in Table 3 and in the text (SD/SE usually refer to normally distributed data).

Is the work clearly and accurately presented and does it cite the current literature?

Yes

Is the study design appropriate and is the work technically sound?

Yes

Are sufficient details of methods and analysis provided to allow replication by others?

Yes

If applicable, is the statistical analysis and its interpretation appropriate?

Yes

Are all the source data underlying the results available to ensure full reproducibility?

Yes

Are the conclusions drawn adequately supported by the results?

Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Pulmonary and Critical Care. Circadian biology. Inflammation

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Author Response 19 May 2022

Tamas Dolinay

We would like to thank the reviewer for his useful comments. Please see below our point-

by-point response:

1. In the revised manuscript, we included the percent of predicted total lung capacity (% of TLC) for our patients (N=20) with standard deviation (SD).
2. We agree with the reviewer that presenting the data with interquartile ranges (IQR) is more representative when used with non-parametric testing. We now show IQR for both Table 3 and 4.

Competing Interests: No competing interests were disclosed.

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