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Residual Lung Disease at 6-month Follow-up CT after COVID-19: Clinical Significance Is a Key Issue

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See also the article by Caruso et al.

Coronavirus Disease 2019 (COVID-19) continues to cause huge numbers of deaths worldwide. Most deaths are due to pulmonary involvement. Survivors of severe COVID-19 pneumonia have a high prevalence of residual abnormalities on thoracic CT. Detailed CT follow-up data after COVID-19 pneumonia now extends to six months after the initial acute episode and beyond. In a recent report, Han et al documented the existence of "fibrotic-like changes" in the lung at six months in over a third of 114 survivors of acute pneumonia **(1)**. In this issue of *Radiology*, Caruso and colleagues **(2)** make a further substantial contribution to the literature by providing multivariable analyses of six-month follow-up CT data after COVID-19 pneumonia. They prospectively enrolled 118 patients with CT abnormalities who received a positive baseline chest CT with a diagnosis of interstitial pneumonia at hospital admission and a confirmed diagnosis of moderate to severe COVID-19. Baseline data, including comorbidities, symptoms, and laboratory findings, were much as expected in a cohort of study participants with ~~severe~~ COVID-19 pneumonia.

The most striking observation was the prevalence of "fibrotic-like" changes at six-month chest CT follow-up in 72% of the study participants in the current study versus 35% in the study by Han et al **(1)**. Mean total lung severity scores, quantified subjectively using a 40-point scale, fell from 15.3 units at baseline to 4.37 units at six months. Calculating exact global measurements is not possible from semi-categorical estimation. But it is clear that on average, abnormalities at six months occupied less than 10% of total lung volume, with many participants having very limited disease. There was similar regression in all lung regions with no obvious predominant regional distribution at six months. However, based on stated standard deviations, a minority of participants had residual abnormalities that would be viewed as clinically significant in a setting of chronic fibrotic lung disease. Individual CT abnormalities decreased in prevalence at follow-up with the notable exception of fibrotic-like abnormalities, seen in 55% of participants at hospital admission and in 72% at six-month follow-up. Importantly, all participants at six-month Chest CT follow-up had either normal scans (28%) or "fibrotic-like" abnormalities (as well as a variable prevalence of other CT

signs). Thus, the existence of “fibrotic-like” abnormalities at six months was synonymous with the presence of residual disease.

The data are complex and should not be overinterpreted. The authors use univariable and stepwise multivariable logistic regression models to identify baseline factors associated with the presence of residual disease in the form of ”fibrotic-like” abnormalities. They constructed three multivariable models: clinical, radiological, and combined. The most robust finding was that residual disease at six months was consistently associated with markers of severe acute lung involvement (need for ventilation in the clinical model, less extensive well-aerated lung in the radiological and combined multivariable models). Other multivariable associations are difficult to interpret, as discussed below. However, it is notable that increasing age was a risk factor for residual disease at six-month follow-up only on univariable analysis and in the clinical multivariable model. The presence of important comorbidities at baseline was not a risk factor in any analysis. Both increasing age and the presence of key comorbidities have consistently been associated with a higher risk of mortality in acute COVID-19. But, if markers of acute pneumonitis severity are included in multivariable analysis, then it appears that increasing age and the presence of key comorbidities are not linked to the presence of residual disease at six months.

These conclusions are helpful in defining the prevalence, features, and major associations with residual disease on CT at six months and are likely to be robust when considered together with other serial CT data post-COVID. However, ambiguities and unanswered questions must be acknowledged. These and other serial CT data do not provide clinicians with knowledge of the prevalence of clinically important residual interstitial lung disease (ILD) post COVID-19. The designation of clinical significance requires the integration of symptoms, pulmonary function abnormalities, and imaging findings: this applies especially to the distinction between interstitial lung abnormalities identified at screening and clinically significant ILD **(3)**. In many patients, it is clear that post-COVID-19 CT abnormalities at six months broadly equate (in extent) with interstitial lung abnormalities and best

management would be ongoing monitoring without the need for interventions considered by clinicians in interstitial lung disease. We believe that in future serial post-COVID CT studies, failure to provide information on symptoms and pulmonary function tests should be viewed as a very major weakness. In particular, given the major regression of disease observed at six months on average, serial symptomatic profiles should also be provided (i.e. information on changes in exercise tolerance with time). Without a multi-dimensional approach, clinical significance cannot be accurately designated.

We also believe that it is time to confront the quasi-fibrotic terminology applied to often limited CT abnormalities post-COVID. Each and every participant with residual disease at six months had a positive "fibrotic-like" score: quite simply, the prediction of "fibrotic-like" abnormalities from baseline data was no more than a prediction of the presence of residual disease. The apparent increase in the prevalence of "fibrotic-like" change at six months is highly deceptive as baseline scans were performed at admission, not when the disease was most severe, and before periods of prolonged ventilation in some of the study participants. A more progressive lung fibrosis hypothesis post-COVID would instead require evaluating change from baseline CT performed at discharge from intensive care or at hospital discharge.

Importantly, the authors acknowledge previous concerns that apparent fibrosis on CT is not synonymous with true fibrosis **(4)**, which is defined histologically. But the ongoing use of the "fibrotic-like" terminology adopted by the authors may create confusion. The Fleischner glossary for CT signs of fibrosis was developed in the setting of chronic fibrotic disease **(5)** and was not based on features on CT during recovery from acute lung injury. Bands, for example, may equally represent atelectasis and limited organizing pneumonia, given that a variably extensive element of organizing pneumonia is evident histologically in acute lung injury.

Even if "fibrotic-like" change on CT does sometimes represent histologic fibrosis, remodeling and regression of immature fibrosis is a likely event following severe acute lung injury. In the current

study, the prevalence of bronchiectasis decreased at follow-up CT: this appears likely to represent regression of "traction bronchiectasis," a reliable irreversible marker of fibrosis in the setting of chronic disease but not, it would seem, in a post-lung injury setting. The authors cite non-COVID-19 post-viral data documenting major decreases in the prevalence of residual disease at one year and longer **(6,7)**. This is equally likely to apply to other forms of acute respiratory distress syndrome (ARDS). Although definitive serial CT studies have not been performed, it is clear from serial pulmonary data that recovery in ARDS survivors is prolonged **(8)**. We call for a moratorium on the use of CT terminology implying the histologic presence of fibrotic disease post-COVID, with the exception of honeycomb change. The term "residual disease" appears sufficient as all study participants with residual disease on CT had "fibrotic-like change" in the current study.

Finally, it may seem harsh to belittle findings on multivariable analysis, other than acknowledging the importance of markers of acute disease severity in all models (the only truly valuable observation arising from this exercise). However, it is difficult to interpret findings when examining a large number of variables in a stepwise model against an insufficiently powered dependent variable (the presence of residual disease). Only 33 study participants did not have residual disease/"fibrotic-like change" at six months. In the combined model, in particular, prior to stepwise elimination, approximately 20 covariates appear to have been included. There is a distinct danger that by chance alone, some variables will be "nuisance variables" (i.e. giving rise to complex spurious inter-relationships), resulting in the removal of key variables by stepwise elimination, a well-recognized problem with stepwise multivariable analysis **(9)**. This may have accounted for important changes in covariate retention in the combined model, compared with the clinical and radiologic models. However, even without the possible retention of "the wrong variables," the clinical value of the multivariable algorithm can be questioned. The models subjected to AUC analysis were not examined against clinically significant residual lung disease at six months and this is perhaps the question most relevant to clinical practice, given the very high prevalence of (often trivial) residual disease.

In summary, in a cohort of 118 study participants with COVID-19 pneumonia, residual disease was apparent on CT in 72% of participants at six-month follow-up. Those with residual disease all had "fibrotic-like" abnormalities on CT. Most CT signs decreased in prevalence at six months: the increase in the prevalence of "fibrotic-like change" is impossible to interpret. Many patients had limited abnormalities at six months with doubtful clinical significance, but in a minority of cases, residual disease was likely to be clinically important. The presence of residual disease at six months was primarily linked to markers of the severity of the acute episode, a uniform finding across multivariable models. The study of Caruso and colleagues is a useful addition to the evidence-based literature. However, there is now a pressing need to gauge the clinical significance of residual disease on CT and to develop predictive models against this end point in future studies. This should ideally be based on longer-term follow-up, without recourse to quasi-fibrotic CT terminology.

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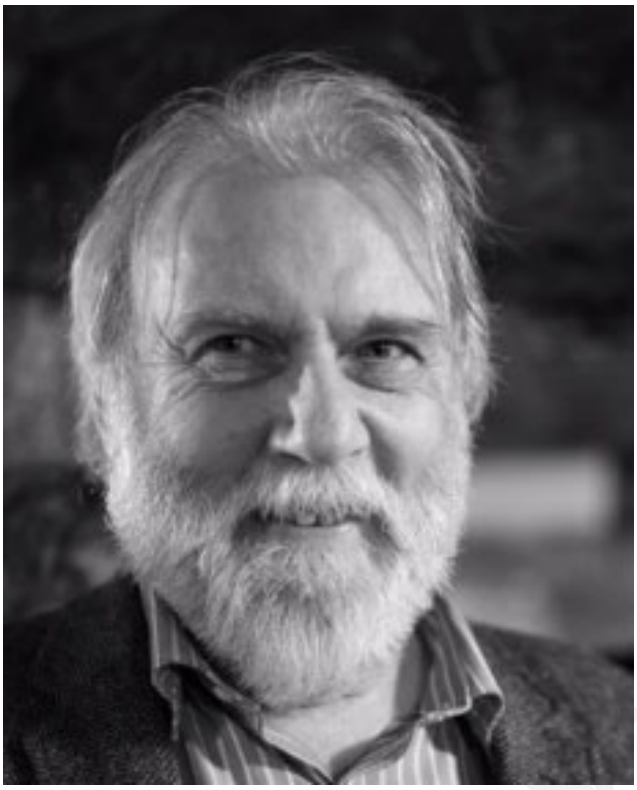

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