Radiology

"In Press" papers have undergone full peer review and have been accepted for publication in Radiology. This article will undergo copyediting, layout, and proof review before it is published in its final version. Please note that during production of the final copyedited article, errors may be discovered which could affect the content.

Long-Term Lung Abnormalities Associated with COVID-19 Pneumonia

Manuscript Type: Review

Jeffrey P. Kanne, M.D. (Corresponding Author)
Department of Radiology
University of Wisconsin School of Medicine and Public Health
Madison, WI
JKanne@uwhealth.org

Brent P. Little, M.D.
Department of Radiology
Mayo Clinic
Jacksonville, FL

Jefree J. Schulte, M.D.
Department of Pathology and Laboratory Medicine
University of Wisconsin School of Medicine and Public Health
Madison, WI

Adina Haramati, M.D.
Department of Radiology
Massachusetts General Hospital
Boston, MA

Linda B. Haramati, M.D., M.S.
Departments of Radiology and Medicine
Montefiore Medical Center
Albert Einstein College of Medicine
Bronx, NY

Abbreviations

ALI – acute lung injury

DAD – diffuse alveolar damage

XeMRI - hyperpolarized Xe^{129} MRI

Summary

Some patients with moderate to severe COVID-19 have chest CT abnormalities that persist at least 1 year after infection and may be associated with symptoms. These CT abnormalities show similarities to those described in the 2002–2003 SARS epidemic.

Essentials

- Approximately one-third of patients hospitalized with COVID-19 pneumonia have abnormalities at chest CT 12 months after infection.
- CT abnormalities range from residual parenchymal bands to fibrosis as well as air trapping and bronchiectasis.
- A very small number of patients have a persistently elevated risk of venothromboembolic disease after acute infection.
- The late histopathologic findings of COVID-19 are similar to those of other causes of acute lung injury with a mix of organizing and chronic fibrosing histologic patterns. Additionally, these findings are comparable to those reported with the SARS epidemic.

Abstract

In the third year of the SARS-CoV-2 pandemic, much has been learned about the long-term effect of COVID-19 pneumonia on the lungs. Approximately one-third of patients with moderate-to-severe pneumonia, especially those requiring intensive care therapy or mechanical ventilation, have residual abnormalities on chest CT one year after presentation. Abnormalities range from parenchymal bands to bronchial dilation to frank fibrosis. Less is known about the long-term pulmonary vascular sequelae, but there appears to be a persistent, increased risk of venothromboembolic events in a small cohort of patients. Finally, the associated histologic abnormalities resulting from SARS-CoV-2 infection are similar to those of patients with other causes of acute lung injury.

Introduction

Now in the third year of the SARS-CoV-2 pandemic and after the most recent wave of the Omicron variant in early 2022, much of the world has shifted to an endemic mode of dealing with COVID-19, albeit unofficially, as the World Health Organization has not declared the pandemic over at the time of this writing. Vaccines are readily available in many countries, and much of the world's population presumably has some degree of immunity from vaccination, previous infection, or both. Unlike SARS-CoV-1, which has not been reported in the community since mid-2003 (1), SARS-CoV-2 does not appear to be fading out to extinction. Even newer variants of SARS-CoV-2 have been shown to escape neutralizing antibodies from previous infection and vaccination (2), contributing to the new infections and reinfections globally.

As the pool of individuals who have suffered one or more episodes of COVID-19 rapidly grows, the proportion of the population with long-term symptoms and chronic lung findings of the disease increases. Post-COVID conditions, also referred to as "long COVID", "long-haul COVID", or "post-acute sequelae of COVID-19", consist of a long list of signs and symptoms ranging from shortness of breath to depression and sleep disturbance (3-5), reported to occur in up to 10% of patients (6-8). While no universally agreed upon definitions exist, The *British Medical Journal* guidelines define long COVID as persistent symptoms after 4 weeks and post-COVID syndrome when symptoms continue beyond 12 weeks (3). While the causes of persistent symptoms are likely multifactorial and currently not well understood, the growing radiology literature on chronic lung findings in COVID-19 may eventually facilitate understanding of long-term respiratory issues and imaging correlates in afflicted individuals.

Familiarity with the typical long-term sequelae of COVID-19 pneumonia on chest imaging is important in evaluating potential causes of chronic respiratory symptoms in survivors, assessing improvement on follow-up imaging, and distinguishing expected post-COVID findings from other lung conditions. This article summarizes current knowledge of post-COVID pulmonary parenchymal, airway, pulmonary vascular, and histopathologic findings.

Lung parenchymal abnormalities

The acute and subacute CT lung parenchymal findings of COVID-19 pneumonia have been well described and are summarized in Table 1. These patterns of lung injury are similar to those of SARS-CoV-1 infection (SARS) (9, 10) and H1N1 influenza (11, 12).

Several prospective observational studies have evaluated the long-term chest CT changes of patients with COVID-19 pneumonia at approximately 12 months after illness (13-27). However, these studies are limited by small cohorts with a wide variety of illness severity. Further complicating matters are differences in follow-up paradigms and CT evaluation methods.

Fortunately, a recent systematic review and meta-analysis by Watanabe et al. provides a better understanding of the observed chest CT findings approximately 12 months after COVID-19 pneumonia (28). The authors aggregated study data from 15 observational (21) studies, providing data on 3134 individuals. One must note that the populations of these studies are quite heterogeneous (heterogeneity statistic, I^2=93%).

Eleven studies were from China, three from Italy, and one from the United Kingdom. In the combined pool of 3134 patients, 1801 patients had CT scans performed at 12 months. Twelve of the 15 studies provided data on the proportion of patients with any residual lung abnormalities on CT, estimated to be 33%. Ground glass opacity (GGO) and “fibrotic-like changes” were the most common findings at 21% each followed by bronchiectasis in 10%, interlobular septal thickening in 8%, reticular opacity in 6%, and consolidation in 3%. “Fibrotic-like changes” varied across studies and included “architectural distortion with traction bronchiectasis, honeycombing, or both” (Figs. 1-3) (15), “traction bronchiectasis/bronchiolectasis, volume loss, or both” (26), “evidence of stripe-like fibrosis but not reticular opacity” (21), and “the presence of honeycombing, reticulation, and traction bronchiectasis” (27).

Twelve of the 15 studies reported the proportion of abnormal chest CT findings at 12 months according to COVID-19 severity. In this subanalyses, 85% of patients with severe/critical COVID-19 (950/1112) and 87% (560/641) with mild/moderate COVID-19 were included. In the severe/critical group, 38% of patients (278 of 816) had residual CT abnormalities including GGO, “fibrotic-like changes”, bronchiectasis, and interlobular septal thickening. In the mild/moderate group, 24% of patients (91 of 378) had residual CT findings consisting mostly of GGO. The results of this systematic review and meta-analysis are similar to results published in 2003 from the SARS-CoV-1 epidemic that showed 30-40% of survivors of SARS had radiologic abnormalities 6-12 months after recovery. Those with residual abnormalities at 12 months had similar findings 15 years later (29, 30).

Confounding full understanding of the long-term chest CT findings of COVID-19 are the many biases and shortcomings in these longitudinal observational studies. Because many studies focus on chest CT scan findings over time, it is not surprising that study cohorts favor patients with more severe disease since they were more likely to undergo chest CT at the time of diagnosis, and patients with mild or no residual abnormalities may not have undergone further imaging. Patients in many of these studies were more likely to be hospitalized and require ICU admission and mechanical ventilation.

Another confounder is that these studies primarily involve patients who contracted COVID-19 in the earlier part of the pandemic. The virus has evolved over time with the more recent, more contagious Omicron variant (BA. 1, BA. 1.1, BA. 2, BA. 3, BA. 4, and BA. 5 lineages) associated with milder disease than the initial variant and the more severe Delta variant (B.1.617.2 and AY lineages). A recent study of 106 hospitalized patients with COVID-19 of whom 40 had the Omicron variant (earlier lineage) and 66 had the Delta variant showed lower CT severity scores in the cohort with the Omicron variant (31). Yoon et al. retrospectively reviewed CT scans of 176 hospitalized patients, 88 with the Delta variant and 88 with early lineage Omicron variant (32). Patients with the Omicron variant had a less severe extent of disease and more of a peribronchial distribution (rather than peripheral) than patients infected with the Delta variant.

The definition of “fibrosis” on chest CT scans used in these studies is also problematic. As highlighted in the systematic review and meta-analysis by Watanabe et al. (28), the definition of “fibrotic like abnormalities” used in some studies varied. Since tissue confirmation of fibrosis was not obtained (appropriately so), the presence of fibrosis is only assumed based on CT findings. Another potential confounder is that patients with residual interstitial lung abnormalities on follow-up CT may have had those abnormalities before COVID-19 pneumonia. These abnormalities have been reported to occur in up to 10% of the population, especially older individuals, who make up the majority of patients with more severe COVID-19 pneumonia (33).

Effects on Airways

Large and small airway abnormalities can be seen in survivors of COVID-19 pneumonia, with frequency and severity correlating with the severity of the acute disease. The acute and subacute CT airway findings of COVID-19 pneumonia are summarized in Table 2. Findings of small airway disease such as mosaic attenuation and air trapping have been seen at paired inspiratory and expiratory CT, and studies of hyperpolarized Xe^{129} MRI (XeMRI) show abnormal ventilation and perfusion patterns in patients with long-COVID respiratory symptoms, even with a normal CT.

Airway abnormalities seen in sequela of previous major respiratory viral outbreaks provide context for the COVID-19 pandemic. In avian-origin influenza (H7N9), bronchiectasis was common at 12-month follow-up CT, present in 24% of patients (10 of 41); restrictive or obstructive PFT abnormalities were found in 55% of patients (11 of 20) for whom 12-month follow-up exams were available (34). Bronchiectasis as a long-term consequence of infection was also seen in MERS and SARS-CoV-1 (35). Air trapping at CT was described as a common finding in survivors of SARS-CoV-1 pneumonia, found in 93% of patients (37 of 40) at a mean follow up of

51.8 days and in 80% (16 of 20) at mean follow up of 140.7 days (35), and in 23% (11 of 47) in another study of 6-month CT in children with SARS-CoV-1 (36).

Large airway abnormalities

Bronchial abnormalities such as wall thickening and dilation are common in patients with COVID-19 pneumonia in the acute and early convalescent phases, decreasing in frequency and severity over time (37). Bronchial dilation persists in a subset of patients after recovery from COVID-19 pneumonia, more frequently in patients with more severe disease, and often as traction bronchiectasis accompanied by other signs of fibrosis. Bronchiectasis after COVID-19 is often peripheral and associated with reticulation or bandlike opacities. Besutti et al. found bronchiectasis on CT in 13% of patients (52 of 405) when performed 5-7 months after discharge for severe COVID-19 pneumonia. Of those, 85% of patients (44 of 52) had a peripheral distribution, while only 2% (1 of 52) had a central distribution, and 13% (7 of 52) had both a central and peripheral distribution (38). As in idiopathic interstitial pneumonias, traction bronchiectasis may be important to recognize because of a correlation with functional impairment. In one study of COVID-19 survivors, traction bronchiectasis was inversely associated with diffusion capacity of the lungs for carbon monoxide (DLCO) percentage predicted ($R = -0.49$, $P<.001$) and FVC percentage predicted ($R = -0.23$, $P = .04$) and was directly correlated with cough scale score ($R = 0.25$, $P = .03$) (39).

Although traction bronchiectasis associated with fibrosis may be an important chronic finding in COVID-19 survivors, existing studies often fail to distinguish traction bronchiectasis (suggesting features of fibrosis) from bronchiectasis broadly construed, which can be caused by any airway injury (Figs. 4-6). For example, in a prospective CT scan study of patients 6 months after discharge for moderate or severe COVID-19 pneumonia, Caruso et al. reported “fibrosis-like changes” defined as “reticulation and/or honeycombing” in 72% of patients (85 of 118), and bronchiectasis in 25% (29 of 118); the percentage of patients with traction bronchiectasis was not reported (40). The meta-analysis by Watanabe et al. similarly includes studies in which the frequencies of traction bronchiectasis and other types of bronchiectasis are unclear (28). These potentially overlapping categories make it difficult to know if bronchiectasis in survivors of COVID-19 represents a primary finding of fibrosis (traction bronchiectasis), airway damage from viral infection or barotrauma, or some combination of these etiologies.

Bronchiectasis has long been recognized as a common finding in ARDS caused by conditions other than COVID-19. Often most extensive in the anterior lungs and accompanied by reticulation and architectural distortion, ARDS-related bronchiectasis is thought to be a product of barotrauma in the setting of mechanical ventilation, with severity correlating with duration of ventilation and high inspiratory pressures (41, 42). Of the 7% of patients (28 of 405) with fibrotic abnormalities in a study of survivors of severe COVID-19 pneumonia, 36% (10 of 28) had “post-ventilatory fibrosis”, defined as anterior predominant subpleural cystic spaces and reticulation, and 90% (9 of 10) of these had traction bronchiectasis (38). Traction bronchiectasis may be primarily due to ARDS and mechanical ventilation: one study of patients hospitalized with moderate COVID-19 pneumonia excluded patients with ARDS, mechanical ventilation, or both found any bronchiectasis or bronchiolectasis on CT at 3 and 12 months in only 2% of patients (2 of 84); “traction bronchiectasis/bronchiolectasis” as a finding of fibrosis was not identified on CT in any patient at 3 months and had developed in only 2% (2 of 84) at 12 months (43).

Bronchial dilation can be completely reversible even from COVID-19 pneumonia complicated by ARDS, underscoring the need for caution in interpreting acute or subacute bronchial dilation as a sign of parenchymal fibrosis or lasting airway damage. In a study of 41 survivors of COVID-19 pneumonia with ARDS, Hu et al. compared CT scans from weeks 1-4 after onset of symptoms to those at least 4 months after infection. Twenty-eight patients (68%) had developed varicoid dilation of bronchi ("traction bronchiectasis") within parenchymal opacities in the first month, which resolved in the majority (21 of 28, 75%) and significantly improved in the remaining 8 patients (20% of the study sample) (44). In a study of patients hospitalized for COVID-19, Pan et al. found dilated bronchi on CT performed at discharge in 27% of patients (57 of 209) and in 11% (24 of 209) at 12 months after symptom onset with resolution of bronchial dilation in the remaining 33 patients (13). Luger et al. found bronchial dilation in 11% of patients (8 of 76) with mild to severe COVID-19 pneumonia at baseline and in 9% (8 of 91) at 12-month follow-up CT (45).

Small airway abnormalities

Recent studies have used paired inspiratory and expiratory CT scans to evaluate the possible contribution of small airway disease to persistent symptoms in long-COVID. Air trapping is defined as the presence of lobules or regions with less than normal increase in attenuation and a lack of decrease in volume on end expiratory CT (46). Although obstructive physiology is much less common than limitations in diffusing capacity (DLCO) in survivors of COVID-19, some patients show evidence of small airway disease at pulmonary function tests, and air trapping on CT may herald small airway disease below the threshold of detection by PFTs (19, 37).

Air trapping is a common finding in acute respiratory infections and has been reported in COVID-19 (47). Air trapping has also been reported as a long-term finding in COVID-19 survivors in several studies. In a study of 205 patients previously hospitalized for COVID-19 pneumonia, air trapping was seen on expiratory CT in 29%, with significantly higher quantitative measures of air trapping in the severe pneumonia than in the mild pneumonia groups (48). Additional studies have examined incidence of air trapping on CT in symptomatic patients with long-COVID. Franquet et al. used paired inspiratory and expiratory CT to assess patients with persistent respiratory symptoms at least 30 days after COVID-19 symptom onset (median 72.5 days); air trapping was the most common abnormality (37/48, 77%) (Fig. 7), more common than other findings such as GGO (19/48, 40%), reticulation (18/48, 38%), or traction bronchiectasis (9/48, 19%); air trapping was more commonly seen in males and increased with age (37). In a prospective study of patients with post-acute sequelae of COVID-19 who had remained symptomatic for at least 30 days following diagnosis, Cho et al. identified air trapping by qualitative inspection in 58% of patients (50 of 86); the authors also used quantitative CT with a supervised machine learning method to assess percentage air trapping within the lungs, finding similar mean values for groups treated in the ambulatory setting (25%), hospitalized patients (25%), and patients who required ICU care (27%). However, patients with COVID-19 had significantly greater mean air trapping than healthy controls (7%, $P<.001$) (49).

It is uncertain if air trapping is a manifestation of reversible airway inflammation, primary airway damage due to COVID-19, postinfectious bronchiolitis obliterans, sequela of DAD, or some other process. Studies of air trapping in COVID-19 survivors have been limited by a lack of comparison CT scans before the onset of infection, precluding the exclusion of preexisting small airway disease. In addition, the presence of air trapping as a common finding in asymptomatic individuals without evidence of small airway disease has been well documented (50).

XeMRI has also recently emerged as a technique for investigating heterogeneity in ventilation and gas transfer in patients with long-COVID symptoms such as breathlessness. 129Xe rapidly diffuses across alveolar membranes and into red blood cells, allowing reconstruction of gas, tissue/plasma, and red blood cell phase images that depict regional ventilation and pulmonary perfusion (51). In a study of 76 COVID-19 survivors (mean of 13.8 weeks after the index positive COVID-19 test) with persistent respiratory symptoms and 9 healthy volunteers without a history of COVID-19, Kooner et al. found significantly greater mean ventilation defect percentages (VDP) in 23 patients previously hospitalized with COVID-19 (8%) than in 53 patients without hospitalization (4%); both groups had significantly higher VDP than healthy volunteers (1%). The same study showed abnormal ratios of residual volume to total lung capacity in 14/38 (37%) of patients for whom it was measured, suggesting small airway obstruction as a cause (52). However, other XeMRI studies have found relatively normal ventilation measured at gas phase, with significant gas exchange deficits as evidenced by abnormal RBC phase images and significantly decreased RBC to tissue plasma ratio, a marker of gas diffusion across alveolar epithelium (51, 53). The relative contributions of small airway disease and alveolar vascular disease are yet to be determined and may vary among individuals and across clinical circumstances.

Pulmonary vascular abnormalities

The presence of pulmonary vascular abnormalities was recognized early in the COVID-19 pandemic. Dilated pulmonary vasculature in regions of pneumonia was described in initial case series (54, 55). Shortly thereafter, elevated risks of pulmonary emboli and *in situ* thrombosis of the pulmonary arteries were noted, especially in patients with severe disease. Over the three years of the pandemic, the spectrum of recognized COVID-19-associated pulmonary vascular disease has greatly broadened, impacting current medical practice.

In this section, we will review contemporary evidence and insights regarding the long-term pulmonary vascular manifestations of SARS-CoV-2 infection with a focus on pulmonary vascular disease in "long COVID". Evolving data related to pulmonary vascular disease in acute COVID-19 are summarized in Table 3. A common thread is pulmonary endotheliitis (56-58), an important feature of acute COVID-19, which can persist in convalesce for an uncertain duration.

"Long COVID" includes a variety of conditions, including PE, that seem to occur at a higher rate among people previously diagnosed with COVID. Bull-Otterson et al. in a retrospective matched cohort study of adults from a national EHR dataset with >63 million records (March 2020-November 2021) followed cohorts for 30-365 days after index encounter for 26 incident conditions described to be associated with "long COVID"

(59). The study cohorts of 353 164 patients with COVID-19 and 1 640 776 without COVID-19 were stratified by age. The COVID-19 cohort had significantly more incident conditions 38% (35.4% for 18-64, 45.4% for ≥65 years) versus 16% (14.6% for 18-64, 18.5% for ≥65 years) compared with the cohort without COVID-19. The highest risk ratio (RR) was for PE, 2.1 and 2.2, respectively for younger and older ages.

The risk of "long-COVID" for patients with breakthrough infections was studied by Ziyad Al-Aly et al. in a retrospective cohort study from the Veterans Affairs database. Those with breakthrough COVID-19 were studied for a variety of the incident conditions described to be associated with "long-COVID" and for mortality. The breakthrough COVID group was compared with contemporary, historical, and unvaccinated controls and patients with seasonal influenza (60). Between 30 days and 6 months after breakthrough COVID, patients had an elevated HR of 1.5 for post-acute COVID-19 conditions with the highest risk (HR~4) for PE; this risk was worst for ICU versus inpatients versus outpatients both overall and for PE. Patients with breakthrough COVID-19 also had a higher risk of death (HR-1.75). Compared with unvaccinated patients with COVID-19 however, these patients had lower risks (long Covid HR-0.85, death HR-0.66). When patients hospitalized with influenza were compared with patients hospitalized with breakthrough COVID, patients with COVID-19 had higher risks of "long-COVID associated" conditions (HR-1.27) and death (HR-2.43).

It is important to distinguish between extremely rare vaccine-associated thrombotic adverse events including PE and PE associated with COVID-19, breakthrough COVID, and long COVID. Vaccine-induced immune thrombotic thrombocytopenic purpura (VITT) is caused by the development of antibodies to platelet factor 4 (PF4) polyanion complexes and has been reported for all four of the major SARS-CoV-2 vaccines in recent use (Pfizer, Moderna, Johnson & Johnson, and AstraZeneca), most frequently for ChADOx1nCoV-19 (AstraZeneca) (61-64). Symptoms typically develop within four weeks of initial vaccination. Recognition of VITT has key therapeutic implications, as heparin is avoided due to the similar mechanism of immune-mediated heparin-induced thrombocytopenia.

The long term pulmonary vascular manifestations of COVID-19 remain incompletely understood. The current consensus favors endotheliitis (56, 65, 66) and extension of the pulmonary inflammatory process (67) rather than vasculitis as the dominant explanation for the wide-ranging COVID-19-associated pulmonary vascular abnormalities. These include a persistently elevated risk of PE and possibly the development of chronic thromboembolic pulmonary hypertension (68) and pulmonary hypertension (69). A variety of intriguing but uncommonly described pulmonary vascular abnormalities have occasionally been reported to be associated with COVID-19 and are of unclear importance. In a small series of ICU patients, Brito-Azevedo et al. described intrapulmonary vascular dilation with shunting on echocardiography, and the authors suggest that this may at least in part be responsible for COVID-19-associated hypoxemia and dilated vessels on CT with a mechanism similar to hepatopulmonary syndrome (70).

Dhawan et al. proposed using lung scintigraphy (V/Q scans) preferably with SPECT as the first line imaging test to assess for residual clot and small pulmonary vessel disease for patients who recovered from COVID-19 but who still have persistent respiratory symptoms (71). Their rationale is that V/Q scans play a leading role in the evaluation of pulmonary small vessel disease, which may be suboptimally demonstrated on CTPA. They highlight the expected patterns of small vessel disease in addition to PE and lung parenchymal disease and suggest that V/Q scans should play a clinical and research role in elucidating the evolution of post-acute COVID-19 vascular disease. Along with V/Q, longitudinal data from spectral CT should continue to shed light on the long term pulmonary vascular sequela of COVID-19 (72).

Pathology of long-term COVID-19

As the COVID-19 pandemic has progressed, the pathologic findings in the lung associated with SARS-CoV-2 infection have slowly materialized. Some of the very first reports of the histopathologic changes in COVID-19 pneumonia from living patients were reported out of Wuhan, China, where patients undergoing lung cancer surgery were also found to have COVID-19 (73). These early reports, unsurprisingly, described changes in acute or early organizing diffuse alveolar damage (DAD) or other patterns of acute lung injury (ALI). Now, in the third year of the pandemic, a clearer picture of the histopathologic changes associated with COVID-19 has emerged.

SARS-CoV-2 infects cells of the human respiratory tract by binding to ACE2 (74). In the acute setting, patients with SARS-CoV-2 and respiratory failure typically have histopathologic findings of DAD; other forms of ALI including organizing pneumonia and acute fibrinous and organizing pneumonia have been reported but are less commonly encountered than DAD. The histopathologic features and pathophysiology of acute COVID-19 pneumonia are beyond the scope of this review and have been well described (75-82). Some authors are of the opinion that acute COVID-19 pathology is similar to other forms of ALI (83, 84), but others suggest that there are findings more commonly present in patients with ALI secondary to COVID-19. While pulmonary microthrombi are often observed as a component of DAD of any cause, they are frequently mentioned as being a prominent finding in acute COVID-19 or occur more often than other viral pneumonias (77, 85-87). Other vascular lesions have been described including old, recanalized thrombi, vascular congestion, and hemangiomatosis-like lesions (Figs. 8-9) in areas without features of ALI (88). While the exact pathophysiology is still debated, these findings suggest the possibility of a distinct vascular phenotype of lung injury occurring in patients with COVID-19.

A patient with DAD, either secondary to COVID-19 or other cause, typically progresses through an acute phase characterized by hyaline membrane formation then to an organizing phase with fibroblast proliferation (Fig. 10) (89). A dichotomy exists in how the lung resolves DAD. While most patients with DAD will have some long-term respiratory symptoms, there may be a gradual resolution of DAD, or the DAD progresses to a fibrotic phase (89, 90).

In the ongoing pandemic, most patients show a complete resolution of pulmonary pathology without histologic evidence of identifiable disease and are unlikely to be imaged further (91). It is now known that this is not true for all patients. Long-term pulmonary sequelae of acute COVID-19 may manifest as organizing pneumonia weeks after initial infection, and this may spontaneously resolve (92). Some of the earliest reports of pulmonary histopathologic changes associated with fibrosis in patients with severe COVID-19 were from explanted lungs from patients who underwent transplant (93, 94). The authors of these studies identified diffuse interstitial fibrosis with rather uniform collagenous thickening of alveolar septa. Honeycomb change was also identified along with cystic spaces lined by histiocytes and giant cells. Some of these findings have also been observed in a lung explant specimen in a preprint article and from an autopsy (95, 96). In a series of transbronchial biopsies from Brazil, septal thickening and airway remodeling were identified (97). Beyond airway remodeling, there are reports of chronic bronchiolitis and peribronchiolar metaplasia (98, 99) These aforementioned cases (93, 94, 97) probably represent the fibrotic phase of DAD and is well described in an autopsy study from China and from a small series of explanted lungs in the US with very similar findings (Fig. 11) (98, 100).

Complicating the histopathologic picture, another series of cases based on surgical lung biopsies, identified usual interstitial pneumonia (UIP) as the pattern of fibrosis in patients with persistent interstitial lung disease following COVID-19 (99). These authors also found other patterns of lung injury, including DAD superimposed upon UIP, desquamative interstitial pneumonia, and acute organizing pneumonia. Last, it should be noted that acute lung injury, especially DAD, is frequently encountered by the pathologist in overlapping stages (i.e. acute on chronic/acute and organizing) (89). Secondary infection can also occur at this phase (Fig. 12) (93). At the time of this writing, the pulmonary pathology community is actively studying the histopathologic findings in “long COVID”, and much is to be said in this area in the near future.

Conclusion

The scientific and medical communities have learned much about diagnosing and treating COVID-19 over two-and-half years since the first cases were reported in Wuhan, China. Although many studies published on the late-term effects of COVID-19, important limitations exist including small numbers for some described entities, and publication biases towards positive studies and severe spectrum disease. Furthermore, “big data” electronic health record studies are prone to selection bias and information bias. The meta-analyses discussed in this review offer some clarity on the data but ultimately are impacted by the variable studies they include.

No consensus currently exists for imaging management of patients with long-term sequelae of COVID-19 pneumonia. A reasonable approach may include inspiratory thin-section chest CT to characterize suspected parenchymal disease, with expiratory imaging as deemed appropriate for assessment of small airway disease. Imaging for suspected acute or chronic PE can be performed with chest CT pulmonary angiography or VQ scan. XeMRI has shown early promise in detecting abnormalities in patients with chronic symptoms and otherwise normal imaging but is considered a research modality and is not widely available. Imaging decisions should be based on patient signs and symptoms, careful clinical evaluation, and the question(s) needed to be answered.

References

1. Centers for Disease Control and Prevention. CDC SARS Response Timeline 2013. Available from: www.cdc.gov/about/history/sars/timeline.htm.
2. Hachmann NP, Miller J, Collier AY, Ventura JD, Yu J, Rowe M, et al. Neutralization Escape by SARS-CoV-2 Omicron Subvariants BA.2.12.1, BA.4, and BA.5. N Engl J Med. 2022. Epub 20220622. doi: 10.1056/NEJMc2206576. PubMed PMID: 35731894.
3. Mahase E. Covid-19: What do we know about "long covid"? BMJ. 2020;370:m2815. Epub 20200714. doi: 10.1136/bmj.m2815. PubMed PMID: 32665317.
4. Hope AA, Evering TH. Postacute Sequelae of Severe Acute Respiratory Syndrome Coronavirus 2 Infection. Infect Dis Clin North Am. 2022;36(2):379-95. Epub 20220215. doi: 10.1016/j.idc.2022.02.004. PubMed PMID: 35636906.
5. Centers for Disease Control and Prevention. Long COVID or Post-COVID conditions 2022 [cited 2022 June 27]. Available from: https://www.cdc.gov/coronavirus/2019-ncov/long-term-effects/index.html.
6. Sudre CH, Murray B, Varsavsky T, Graham MS, Penfold RS, Bowyer RC, et al. Attributes and predictors of long COVID. Nat Med. 2021;27(4):626-31. Epub 20210310. doi: 10.1038/s41591-021-01292-y. PubMed PMID: 33692530; PubMed Central PMCID: PMC7611399.
7. Greenhalgh T, Knight M, A'Court C, Buxton M, Husain L. Management of post-acute covid-19 in primary care. BMJ. 2020;370:m3026. Epub 20200811. doi: 10.1136/bmj.m3026. PubMed PMID: 32784198.
8. Xie Y, Bowe B, Al-Aly Z. Burdens of post-acute sequelae of COVID-19 by severity of acute infection, demographics and health status. Nat Commun. 2021;12(1):6571. Epub 20211112. doi: 10.1038/s41467-021-26513-3. PubMed PMID: 34772922; PubMed Central PMCID: PMC8589966.
9. Müller NL, Ooi GC, Khong PL, Zhou LJ, Tsang KWT, Nicolaou S. High-Resolution CT Findings of Severe Acute Respiratory Syndrome at Presentation and After Admission. American Journal of Roentgenology. 2004;182(1):39-44. doi: 10.2214/ajr.182.1.1820039.
10. Ketai L, Paul NS, Wong K-tT. Radiology of Severe Acute Respiratory Syndrome (SARS): The Emerging Pathologic-Radiologic Correlates of an Emerging Disease. Journal of Thoracic Imaging. 2006;21(4).
11. Ajlan AM, Quiney B, Nicolaou S, Müller NL. Swine-origin influenza A (H1N1) viral infection: radiographic and CT findings. AJR Am J Roentgenol. 2009;193(6):1494-9. doi: 10.2214/AJR.09.3625. PubMed PMID: 19933639.
12. Marchiori E, Zanetti G, D'Ippolito G, Verrastro CG, Meirelles GS, Capobianco J, et al. Swine-origin influenza A (H1N1) viral infection: thoracic findings on CT. AJR Am J Roentgenol. 2011;196(6):W723-8. doi: 10.2214/AJR.10.5109. PubMed PMID: 21606260.
13. Pan F, Yang L, Liang B, Ye T, Li L, Liu D, et al. Chest CT Patterns from Diagnosis to 1 Year of Follow-up in Patients with COVID-19. Radiology. 2022;302(3):709-19. Epub 20211005. doi: 10.1148/radiol.2021211199. PubMed PMID: 34609153; PubMed Central PMCID: PMC8515211.
14. Wu X, Liu X, Zhou Y, Yu H, Li R, Zhan Q, 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. Epub 20210505. doi: 10.1016/S2213-2600(21)00174-0. PubMed PMID: 33964245; PubMed Central PMCID: PMC8099316.
15. Han X, Fan Y, Alwalid O, Zhang X, Jia X, Zheng Y, et al. Fibrotic Interstitial Lung Abnormalities at 1-year Follow-up CT after Severe COVID-19. Radiology. 2021;301(3):E438-E40. Epub 20210727. doi: 10.1148/radiol.2021210972. PubMed PMID: 34313470; PubMed Central PMCID: PMC8335811.
16. Chen Y, Ding C, Yu L, Guo W, Feng X, Su J, et al. One-year follow-up of chest CT findings in patients after SARS-CoV-2 infection. BMC Med. 2021;19(1):191. Epub 20210809. doi: 10.1186/s12916-021-02056-8. PubMed PMID: 34365975; PubMed Central PMCID: PMC8349604.
17. Huang L, Yao Q, Gu X, Wang Q, Ren L, Wang Y, et al. 1-year outcomes in hospital survivors with COVID-19: a longitudinal cohort study. Lancet. 2021;398(10302):747-58. doi: 10.1016/S0140-6736(21)01755-4. PubMed PMID: 34454673; PubMed Central PMCID: PMC8389999.
18. Shang L, Wang L, Zhou F, Li J, Liu Y, Yang S. Long-term effects of obesity on COVID-19 patients discharged from hospital. Immun Inflamm Dis. 2021;9(4):1678-85. Epub 20210909. doi: 10.1002/iid3.522. PubMed PMID: 34499804; PubMed Central PMCID: PMC8589408.
19. Zhao Y, Yang C, An X, Xiong Y, Shang Y, He J, et al. Follow-up study on COVID-19 survivors one year after discharge from hospital. Int J Infect Dis. 2021;112:173-82. Epub 20210912. doi: 10.1016/j.ijid.2021.09.017. PubMed PMID: 34520845; PubMed Central PMCID: PMC8434916.
20. Zhan Y, Zhu Y, Wang S, Jia S, Gao Y, Lu Y, et al. SARS-CoV-2 immunity and functional recovery of COVID-19 patients 1-year after infection. Signal Transduct Target Ther. 2021;6(1):368. Epub 20211013. doi: 10.1038/s41392-021-00777-z. PubMed PMID: 34645784; PubMed Central PMCID: PMC8512652.
21. Liao T, Meng D, Xiong L, Wu S, Yang L, Wang S, et al. Long-Term Effects of COVID-19 on Health Care Workers 1-Year Post-Discharge in Wuhan. Infect Dis Ther. 2022;11(1):145-63. Epub 20211023. doi: 10.1007/s40121-021-00553-0. PubMed PMID: 34687442; PubMed Central PMCID: PMC8536919.
22. Gamberini L, Mazzoli CA, Prediletto I, Sintonen H, Scaramuzzo G, Allegri D, et al. Health-related quality of life profiles, trajectories, persistent symptoms and pulmonary function one year after ICU discharge in invasively ventilated COVID-19 patients, a prospective follow-up study. Respir Med. 2021;189:106665. Epub 20211022. doi: 10.1016/j.rmed.2021.106665. PubMed PMID: 34717097; PubMed Central PMCID: PMC8531241.
23. Bellan M, Baricich A, Patrucco F, Zeppegno P, Gramaglia C, Balbo PE, et al. Long-term sequelae are highly prevalent one year after hospitalization for severe COVID-19. Sci Rep. 2021;11(1):22666. Epub 20211122. doi: 10.1038/s41598-021-01215-4. PubMed PMID: 34811387; PubMed Central PMCID: PMC8608998.
24. Zhou F, Tao M, Shang L, Liu Y, Pan G, Jin Y, et al. Assessment of Sequelae of COVID-19 Nearly 1 Year After Diagnosis. Front Med (Lausanne). 2021;8:717194. Epub 20211123. doi: 10.3389/fmed.2021.717194. PubMed PMID: 34888318; PubMed Central PMCID: PMC8649686.

25. Li Y, Han X, Huang J, Alwalid O, Jia X, Yuan M, et al. Follow-up study of pulmonary sequelae in discharged COVID-19 patients with diabetes or secondary hyperglycemia. Eur J Radiol. 2021;144:109997. Epub 20211009. doi: 10.1016/j.ejrad.2021.109997. PubMed PMID: 34634534; PubMed Central PMCID: PMC8500791.
26. Vijayakumar B, Tonkin J, Devaraj A, Philip KEJ, Orton CM, Desai SR, et al. CT Lung Abnormalities after COVID-19 at 3 Months and 1 Year after Hospital Discharge. Radiology. 2022;303(2):444-54. Epub 20211005. doi: 10.1148/radiol.2021211746. PubMed PMID: 34609195; PubMed Central PMCID: PMC8515207.
27. Zangrillo A, Belletti A, Palumbo D, Calvi MR, Guzzo F, Fominskiy EV, et al. One-Year Multidisciplinary Follow-Up of Patients With COVID-19 Requiring Invasive Mechanical Ventilation. J Cardiothorac Vasc Anesth. 2022;36(5):1354-63. Epub 20211127. doi: 10.1053/j.jvca.2021.11.032. PubMed PMID: 34973891; PubMed Central PMCID: PMC8626145.
28. Watanabe A, So M, Iwagami M, Fukunaga K, Takagi H, Kabata H, et al. One-year follow-up CT findings in COVID-19 patients: A systematic review and meta-analysis. Respirology. 2022. Epub 20220612. doi: 10.1111/resp.14311. PubMed PMID: 35694728.
29. Zhang P, Li J, Liu H, Han N, Ju J, Kou Y, et al. Long-term bone and lung consequences associated with hospital-acquired severe acute respiratory syndrome: a 15-year follow-up from a prospective cohort study. Bone Res. 2020;8:8. Epub 20200214. doi: 10.1038/s41413-020-0084-5. PubMed PMID: 32128276; PubMed Central PMCID: PMC7018717.
30. Hui DS, Joynt GM, Wong KT, Gomersall CD, Li TS, Antonio G, et al. Impact of severe acute respiratory syndrome (SARS) on pulmonary function, functional capacity and quality of life in a cohort of survivors. Thorax. 2005;60(5):401-9. doi: 10.1136/thx.2004.030205. PubMed PMID: 15860716; PubMed Central PMCID: PMC1758905.
31. Tsakok MT, Watson RA, Saujani SJ, Kong M, Xie C, Peschl H, et al. Chest CT and Hospital Outcomes in Patients with Omicron Compared with Delta Variant SARS-CoV-2 Infection. Radiology. 2022:220533. Epub 20220621. doi: 10.1148/radiol.220533. PubMed PMID: 35727150.
32. Yoon SH, Lee JH, Kim BN. Chest CT Findings in Hospitalized Patients with SARS-CoV-2: Delta versus Omicron Variants. Radiology. 2022:220676. Epub 20220628. doi: 10.1148/radiol.220676. PubMed PMID: 35762887.
33. Hata A, Schiebler ML, Lynch DA, Hatabu H. Interstitial Lung Abnormalities: State of the Art. Radiology. 2021;301(1):19-34. Epub 20210810. doi: 10.1148/radiol.2021204367. PubMed PMID: 34374589; PubMed Central PMCID: PMC8487219.
34. Chen J, Wu J, Hao S, Yang M, Lu X, Chen X, et al. Long term outcomes in survivors of epidemic Influenza A (H7N9) virus infection. Sci Rep. 2017;7(1):17275. Epub 20171208. doi: 10.1038/s41598-017-17497-6. PubMed PMID: 29222500; PubMed Central PMCID: PMC5722861.
35. Chang YC, Yu CJ, Chang SC, Galvin JR, Liu HM, Hsiao CH, et al. Pulmonary sequelae in convalescent patients after severe acute respiratory syndrome: evaluation

with thin-section CT. Radiology. 2005;236(3):1067-75. Epub 20050729. doi: 10.1148/radiol.2363040958. PubMed PMID: 16055695.
36. Chu WC, Li AM, Ng AW, So HK, Lam WW, Lo KL, et al. Thin-Section CT 12 Months After the Diagnosis of Severe Acute Respiratory Syndrome in Pediatric Patients. AJR Am J Roentgenol. 2006;186(6):1707-14. doi: 10.2214/AJR.05.0382. PubMed PMID: 16714663.
37. Franquet T, Giménez A, Ketai L, Mazzini S, Rial A, Pomar V, et al. Air trapping in COVID-19 patients following hospital discharge: retrospective evaluation with paired inspiratory/expiratory thin-section CT. Eur Radiol. 2022;32(7):4427-36. Epub 20220228. doi: 10.1007/s00330-022-08580-2. PubMed PMID: 35226158; PubMed Central PMCID: PMC8884095.
38. Besutti G, Monelli F, Schirò S, Milone F, Ottone M, Spaggiari L, et al. Follow-Up CT Patterns of Residual Lung Abnormalities in Severe COVID-19 Pneumonia Survivors: A Multicenter Retrospective Study. Tomography. 2022;8(3):1184-95. Epub 20220420. doi: 10.3390/tomography8030097. PubMed PMID: 35645383.
39. McGroder CF, Zhang D, Choudhury MA, Salvatore MM, D'Souza BM, Hoffman EA, et al. Pulmonary fibrosis 4 months after COVID-19 is associated with severity of illness and blood leucocyte telomere length. Thorax. 2021;76(12):1242-5. Epub 20210429. doi: 10.1136/thoraxjnl-2021-217031. PubMed PMID: 33927016; PubMed Central PMCID: PMC8103561.
40. Caruso D, Guido G, Zerunian M, Polidori T, Lucertini E, Pucciarelli F, et al. Post-Acute Sequelae of COVID-19 Pneumonia: Six-month Chest CT Follow-up. Radiology. 2021;301(2):E396-E405. Epub 20210727. doi: 10.1148/radiol.2021210834. PubMed PMID: 34313468; PubMed Central PMCID: PMC8335814.
41. Treggiari MM, Romand JA, Martin JB, Suter PM. Air cysts and bronchiectasis prevail in nondependent areas in severe acute respiratory distress syndrome: a computed tomographic study of ventilator-associated changes. Crit Care Med. 2002;30(8):1747-52. doi: 10.1097/00003246-200208000-00012. PubMed PMID: 12163787.
42. Desai SR, Wells AU, Rubens MB, Evans TW, Hansell DM. Acute respiratory distress syndrome: CT abnormalities at long-term follow-up. Radiology. 1999;210(1):29-35. Epub 1999/01/14. doi: 10.1148/radiology.210.1.r99ja2629. PubMed PMID: 9885583.
43. Bocchino M, Lieto R, Romano F, Sica G, Bocchini G, Muto E, et al. Chest CT-based Assessment of 1-year Outcomes after Moderate COVID-19 Pneumonia. Radiology. 2022:220019. Epub 20220510. doi: 10.1148/radiol.220019. PubMed PMID: 35536134.
44. Hu Q, Liu Y, Chen C, Sun Z, Wang Y, Xiang M, et al. Reversible Bronchiectasis in COVID-19 Survivors With Acute Respiratory Distress Syndrome: Pseudobronchiectasis. Front Med (Lausanne). 2021;8:739857. Epub 20211130. doi: 10.3389/fmed.2021.739857. PubMed PMID: 34917630; PubMed Central PMCID: PMC8669592.
45. Luger AK, Sonnweber T, Gruber L, Schwabl C, Cima K, Tymoszuk P, et al. Chest CT of Lung Injury 1 Year after COVID-19 Pneumonia: The CovILD Study. Radiology. 2022:211670. Epub 20220329. doi: 10.1148/radiol.211670. PubMed PMID: 35348379; PubMed Central PMCID: PMC8988857.

46. Hansell DM, Bankier AA, MacMahon H, McLoud TC, Müller NL, Remy J. Fleischner Society: glossary of terms for thoracic imaging. Radiology. 2008;246(3):697-722. Epub 20080114. doi: 10.1148/radiol.2462070712. PubMed PMID: 18195376.
47. Costa RD, Zanon M, Watte G, Altmayer SPL, Mohammed TL, Verma N, et al. Expiratory CT scanning in COVID-19 patients: can we add useful data? J Bras Pneumol. 2022;48(2):e20210204. Epub 20220420. doi: 10.36416/1806-3756/e20210204. PubMed PMID: 35475863; PubMed Central PMCID: PMC9064648.
48. Jia X, Han X, Cao Y, Fan Y, Yuan M, Li Y, et al. Quantitative inspiratory-expiratory chest CT findings in COVID-19 survivors at the 6-month follow-up. Sci Rep. 2022;12(1):7402. Epub 20220505. doi: 10.1038/s41598-022-11237-1. PubMed PMID: 35513692; PubMed Central PMCID: PMC9070972.
49. Cho JL, Villacreses R, Nagpal P, Guo J, Pezzulo AA, Thurman AL, et al. Quantitative Chest CT Assessment of Small Airways Disease in Post-Acute SARS-CoV-2 Infection. Radiology. 2022;304(1):185-92. Epub 20220315. doi: 10.1148/radiol.212170. PubMed PMID: 35289657.
50. Tanaka N, Matsumoto T, Miura G, Emoto T, Matsunaga N, Ueda K, et al. Air trapping at CT: high prevalence in asymptomatic subjects with normal pulmonary function. Radiology. 2003;227(3):776-85. Epub 20030417. doi: 10.1148/radiol.2273020352. PubMed PMID: 12702825.
51. Grist JT, Collier GJ, Walters H, Kim M, Chen M, Abu Eid G, et al. Lung Abnormalities Depicted with Hyperpolarized Xenon MRI in Patients with Long COVID. Radiology. 2022:220069. Epub 20220524. doi: 10.1148/radiol.220069. PubMed PMID: 35608443.
52. Kooner HK, McIntosh MJ, Matheson AM, Venegas C, Radadia N, Ho T, et al. Xe MRI ventilation defects in ever-hospitalised and never-hospitalised people with post-acute COVID-19 syndrome. BMJ Open Respir Res. 2022;9(1). doi: 10.1136/bmjresp-2022-001235. PubMed PMID: 35584850.
53. Grist JT, Chen M, Collier GJ, Raman B, Abueid G, McIntyre A, et al. Hyperpolarized. Radiology. 2021;301(1):E353-E60. Epub 20210525. doi: 10.1148/radiol.2021210033. PubMed PMID: 34032513; PubMed Central PMCID: PMC8168952.
54. Li Y, Xia L. Coronavirus Disease 2019 (COVID-19): Role of Chest CT in Diagnosis and Management. AJR Am J Roentgenol. 2020;214(6):1280-6. Epub 20200304. doi: 10.2214/AJR.20.22954. PubMed PMID: 32130038.
55. Lang M, Som A, Carey D, Reid N, Mendoza DP, Flores EJ, et al. Pulmonary Vascular Manifestations of COVID-19 Pneumonia. Radiol Cardiothorac Imaging. 2020;2(3):e200277. Epub 20200618. doi: 10.1148/ryct.2020200277. PubMed PMID: 34036264; PubMed Central PMCID: PMC7307217.
56. Alnima T, Mulder MMG, van Bussel BCT, Ten Cate H. COVID-19 Coagulopathy: From Pathogenesis to Treatment. Acta Haematol. 2022;145(3):282-96. Epub 20220208. doi: 10.1159/000522498. PubMed PMID: 35499460; PubMed Central PMCID: PMC9059042.
57. Fogarty H, Townsend L, Morrin H, Ahmad A, Comerford C, Karampini E, et al. Persistent endotheliopathy in the pathogenesis of long COVID syndrome. J Thromb Haemost. 2021;19(10):2546-53. Epub 20210912. doi: 10.1111/jth.15490. PubMed PMID: 34375505; PubMed Central PMCID: PMC8420256.

58. Ambrosino P, Calcaterra I, Molino A, Moretta P, Lupoli R, Spedicato GA, et al. Persistent Endothelial Dysfunction in Post-Acute COVID-19 Syndrome: A Case-Control Study. Biomedicines. 2021;9(8). Epub 20210804. doi: 10.3390/biomedicines9080957. PubMed PMID: 34440161; PubMed Central PMCID: PMC8391623.
59. L B-O, S B, S S, TK B, S A, S G, et al. Post–COVID Conditions Among Adult COVID-19 Survivors Aged 18–64 and ≥65 Years — United States, March 2020–November 2021. Atlanta, GA: Centers for Disease Control and Prevention, 2022.
60. Al-Aly Z, Bowe B, Xie Y. Long COVID after breakthrough SARS-CoV-2 infection. Nat Med. 2022. Epub 20220525. doi: 10.1038/s41591-022-01840-0. PubMed PMID: 35614233.
61. Tobaiqy M, MacLure K, Elkout H, Stewart D. Thrombotic Adverse Events Reported for Moderna, Pfizer and Oxford-AstraZeneca COVID-19 Vaccines: Comparison of Occurrence and Clinical Outcomes in the EudraVigilance Database. Vaccines (Basel). 2021;9(11). Epub 20211115. doi: 10.3390/vaccines9111326. PubMed PMID: 34835256; PubMed Central PMCID: PMC8624459.
62. Matar RH, Than CA, Nakanishi H, Daniel RS, Smayra K, Sim BL, et al. Outcomes of patients with thromboembolic events following coronavirus disease 2019 AstraZeneca vaccination: a systematic review and meta-analysis. Blood Coagul Fibrinolysis. 2022;33(2):90-112. doi: 10.1097/MBC.0000000000001113. PubMed PMID: 34980833; PubMed Central PMCID: PMC8815637.
63. Gangi A, Mobashwera B, Ganczakowski M, Ayto R. Imaging and Hematologic Findings in Thrombosis and Thrombocytopenia after ChAdOx1 nCoV-19 (AstraZeneca) Vaccination. Radiology. 2021;301(2):E416. doi: 10.1148/radiol.2021219018. PubMed PMID: 34694936; PubMed Central PMCID: PMC8906350.
64. Curcio R, Gandolfo V, Alcidi R, Giacomino L, Campanella T, Casarola G, et al. Vaccine-induced massive pulmonary embolism and thrombocytopenia following a single dose of Janssen Ad26.COV2.S vaccination. Int J Infect Dis. 2022;116:154-6. Epub 20220102. doi: 10.1016/j.ijid.2021.12.345. PubMed PMID: 34986404; PubMed Central PMCID: PMC8720302.
65. Thacker VV, Sharma K, Dhar N, Mancini GF, Sordet-Dessimoz J, McKinney JD. Rapid endotheliitis and vascular damage characterize SARS-CoV-2 infection in a human lung-on-chip model. EMBO Rep. 2021;22(6):e52744. Epub 20210527. doi: 10.15252/embr.202152744. PubMed PMID: 33908688; PubMed Central PMCID: PMC8183417.
66. Korompoki E, Gavriatopoulou M, Fotiou D, Ntanasis-Stathopoulos I, Dimopoulos MA, Terpos E. Late-onset hematological complications post COVID-19: An emerging medical problem for the hematologist. Am J Hematol. 2022;97(1):119-28. Epub 20211108. doi: 10.1002/ajh.26384. PubMed PMID: 34687462; PubMed Central PMCID: PMC8646944.
67. Giryes S, Bragazzi NL, Bridgewood C, De Marco G, McGonagle D. COVID-19 Vasculitis and vasculopathy-Distinct immunopathology emerging from the close juxtaposition of Type II Pneumocytes and Pulmonary Endothelial Cells. Semin Immunopathol. 2022;44(3):375-90. Epub 20220412. doi: 10.1007/s00281-022-00928-6. PubMed PMID: 35412072; PubMed Central PMCID: PMC9003176.
68. Cueto-Robledo G, Roldan-Valadez E, Graniel-Palafox LE, Garcia-Cesar M, Torres-Rojas MB, Enriquez-Garcia R, et al. Chronic Thromboembolic Pulmonary

Hypertension (CTEPH): A Review of Another Sequel of Severe Post-Covid-19 Pneumonia. Curr Probl Cardiol. 2022:101187. Epub 20220325. doi: 10.1016/j.cpcardiol.2022.101187. PubMed PMID: 35346727; PubMed Central PMCID: PMC8956357.
69. Tudoran C, Tudoran M, Lazureanu VE, Marinescu AR, Pop GN, Pescariu AS, et al. Evidence of Pulmonary Hypertension after SARS-CoV-2 Infection in Subjects without Previous Significant Cardiovascular Pathology. J Clin Med. 2021;10(2). Epub 20210107. doi: 10.3390/jcm10020199. PubMed PMID: 33430492; PubMed Central PMCID: PMC7827420.
70. Brito-Azevedo A, Pinto EC, de Cata Preta Corrêa GA, Bouskela E. SARS-CoV-2 infection causes pulmonary shunt by vasodilatation. J Med Virol. 2021;93(1):573-5. Epub 20200802. doi: 10.1002/jmv.26342. PubMed PMID: 32706407; PubMed Central PMCID: PMC7404894.
71. Dhawan RT, Gopalan D, Howard L, Vicente A, Park M, Manalan K, et al. Beyond the clot: perfusion imaging of the pulmonary vasculature after COVID-19. Lancet Respir Med. 2021;9(1):107-16. Epub 20201117. doi: 10.1016/S2213-2600(20)30407-0. PubMed PMID: 33217366; PubMed Central PMCID: PMC7833494.
72. Salerno D, Oriaku I, Darnell M, Lanclus M, De Backer J, Lavon B, et al. Association of abnormal pulmonary vasculature on CT scan for COVID-19 infection with decreased diffusion capacity in follow up: A retrospective cohort study. PLoS One. 2021;16(10):e0257892. Epub 20211015. doi: 10.1371/journal.pone.0257892. PubMed PMID: 34653196; PubMed Central PMCID: PMC8519442.
73. Tian S, Hu W, Niu L, Liu H, Xu H, Xiao SY. Pulmonary Pathology of Early-Phase 2019 Novel Coronavirus (COVID-19) Pneumonia in Two Patients With Lung Cancer. J Thorac Oncol. 2020;15(5):700-4. Epub 20200228. doi: 10.1016/j.jtho.2020.02.010. PubMed PMID: 32114094; PubMed Central PMCID: PMC7128866.
74. Lan J, Ge J, Yu J, Shan S, Zhou H, Fan S, et al. Structure of the SARS-CoV-2 spike receptor-binding domain bound to the ACE2 receptor. Nature. 2020;581(7807):215-20. Epub 20200330. doi: 10.1038/s41586-020-2180-5. PubMed PMID: 32225176.
75. Borczuk AC. Pulmonary pathology of COVID-19: a review of autopsy studies. Curr Opin Pulm Med. 2021;27(3):184-92. doi: 10.1097/MCP.0000000000000761. PubMed PMID: 33399353.
76. Wiersinga WJ, Rhodes A, Cheng AC, Peacock SJ, Prescott HC. Pathophysiology, Transmission, Diagnosis, and Treatment of Coronavirus Disease 2019 (COVID-19): A Review. JAMA. 2020;324(8):782-93. doi: 10.1001/jama.2020.12839. PubMed PMID: 32648899.
77. Bösmüller H, Matter M, Fend F, Tzankov A. The pulmonary pathology of COVID-19. Virchows Arch. 2021;478(1):137-50. Epub 20210219. doi: 10.1007/s00428-021-03053-1. PubMed PMID: 33604758; PubMed Central PMCID: PMC7892326.
78. Peiris S, Mesa H, Aysola A, Manivel J, Toledo J, Borges-Sa M, et al. Pathological findings in organs and tissues of patients with COVID-19: A systematic review. PLoS One. 2021;16(4):e0250708. Epub 20210428. doi: 10.1371/journal.pone.0250708. PubMed PMID: 33909679; PubMed Central PMCID: PMC8081217.
79. Satturwar S, Fowkes M, Farver C, Wilson AM, Eccher A, Girolami I, et al. Postmortem Findings Associated With SARS-CoV-2: Systematic Review and Meta-

analysis. Am J Surg Pathol. 2021;45(5):587-603. doi: 10.1097/PAS.0000000000001650. PubMed PMID: 33481385; PubMed Central PMCID: PMC8132567.
80. Vasquez-Bonilla WO, Orozco R, Argueta V, Sierra M, Zambrano LI, Muñoz-Lara F, et al. A review of the main histopathological findings in coronavirus disease 2019. Hum Pathol. 2020;105:74-83. Epub 20200802. doi: 10.1016/j.humpath.2020.07.023. PubMed PMID: 32750378; PubMed Central PMCID: PMC7395947.
81. Calabrese F, Pezzuto F, Fortarezza F, Hofman P, Kern I, Panizo A, et al. Pulmonary pathology and COVID-19: lessons from autopsy. The experience of European Pulmonary Pathologists. Virchows Arch. 2020;477(3):359-72. Epub 20200709. doi: 10.1007/s00428-020-02886-6. PubMed PMID: 32642842; PubMed Central PMCID: PMC7343579.
82. Borczuk AC, Salvatore SP, Seshan SV, Patel SS, Bussel JB, Mostyka M, et al. COVID-19 pulmonary pathology: a multi-institutional autopsy cohort from Italy and New York City. Mod Pathol. 2020;33(11):2156-68. Epub 20200902. doi: 10.1038/s41379-020-00661-1. PubMed PMID: 32879413; PubMed Central PMCID: PMC7463226.
83. Konopka KE, Nguyen T, Jentzen JM, Rayes O, Schmidt CJ, Wilson AM, et al. Diffuse alveolar damage (DAD) resulting from coronavirus disease 2019 Infection is Morphologically Indistinguishable from Other Causes of DAD. Histopathology. 2020;77(4):570-8. Epub 20200912. doi: 10.1111/his.14180. PubMed PMID: 32542743; PubMed Central PMCID: PMC7323403.
84. McMullen P, Pytel P, Snyder A, Smith H, Vickery J, Brainer J, et al. A series of COVID-19 autopsies with clinical and pathologic comparisons to both seasonal and pandemic influenza. J Pathol Clin Res. 2021;7(5):459-70. Epub 20210507. doi: 10.1002/cjp2.220. PubMed PMID: 33960723; PubMed Central PMCID: PMC8239851.
85. Hariri LP, North CM, Shih AR, Israel RA, Maley JH, Villalba JA, et al. Lung Histopathology in Coronavirus Disease 2019 as Compared With Severe Acute Respiratory Sydrome and H1N1 Influenza: A Systematic Review. Chest. 2021;159(1):73-84. Epub 20201007. doi: 10.1016/j.chest.2020.09.259. PubMed PMID: 33038391; PubMed Central PMCID: PMC7538870.
86. Parra-Medina R, Herrera S, Mejia J. Systematic Review of Microthrombi in COVID-19 Autopsies. Acta Haematol. 2021;144(5):476-83. Epub 20210419. doi: 10.1159/000515104. PubMed PMID: 33873184; PubMed Central PMCID: PMC8089413.
87. Jonigk D, Werlein C, Lee PD, Kauczor HU, Länger F, Ackermann M. Pulmonary and Systemic Pathology in COVID-19-Holistic Pathological Analyses. Dtsch Arztebl Int. 2022(Forthcoming). Epub 20220624. doi: 10.3238/arztebl.m2022.0231. PubMed PMID: 35698804.
88. De Michele S, Sun Y, Yilmaz MM, Katsyv I, Salvatore M, Dzierba AL, et al. Forty Postmortem Examinations in COVID-19 Patients. Am J Clin Pathol. 2020;154(6):748-60. doi: 10.1093/ajcp/aqaa156. PubMed PMID: 32876680; PubMed Central PMCID: PMC7499554.
89. Beasley MB. The pathologist's approach to acute lung injury. Arch Pathol Lab Med. 2010;134(5):719-27. doi: 10.5858/134.5.719. PubMed PMID: 20441502.

90. Katzenstein AL, Bloor CM, Leibow AA. Diffuse alveolar damage--the role of oxygen, shock, and related factors. A review. Am J Pathol. 1976;85(1):209-28. PubMed PMID: 788524; PubMed Central PMCID: PMC2032554.
91. Diaz A, Bujnowski D, McMullen P, Lysandrou M, Ananthanarayanan V, Husain AN, et al. Pulmonary Parenchymal Changes in COVID-19 Survivors. Ann Thorac Surg. 2022;114(1):301-10. Epub 20210731. doi: 10.1016/j.athoracsur.2021.06.076. PubMed PMID: 34343471; PubMed Central PMCID: PMC8325553.
92. Funk GC, Nell C, Pokieser W, Thaler B, Rainer G, Valipour A. Organizing pneumonia following Covid19 pneumonia. Wien Klin Wochenschr. 2021;133(17-18):979-82. Epub 20210416. doi: 10.1007/s00508-021-01852-9. PubMed PMID: 33861398; PubMed Central PMCID: PMC8050821.
93. Aesif SW, Bribriesco AC, Yadav R, Nugent SL, Zubkus D, Tan CD, et al. Pulmonary Pathology of COVID-19 Following 8 Weeks to 4 Months of Severe Disease: A Report of Three Cases, Including One With Bilateral Lung Transplantation. Am J Clin Pathol. 2021;155(4):506-14. doi: 10.1093/ajcp/aqaa264. PubMed PMID: 33316056; PubMed Central PMCID: PMC7799292.
94. Hall DJ, Schulte JJ, Lewis EE, Bommareddi SR, Rohrer CT, Sultan S, et al. Successful Lung Transplantation for Severe Post-COVID-19 Pulmonary Fibrosis. Ann Thorac Surg. 2022;114(1):e17-e9. Epub 20211105. doi: 10.1016/j.athoracsur.2021.10.004. PubMed PMID: 34748736; PubMed Central PMCID: PMC8570389.
95. Bharat A, Querrey M, Markov NS, Kim S, Kurihara C, Garza-Castillon R, et al. Lung transplantation for pulmonary fibrosis secondary to severe COVID-19. medRxiv. 2020. Epub 20201027. doi: 10.1101/2020.10.26.20218636. PubMed PMID: 33140069; PubMed Central PMCID: PMC7605582.
96. Schwensen HF, Borreschmidt LK, Storgaard M, Redsted S, Christensen S, Madsen LB. Fatal pulmonary fibrosis: a post-COVID-19 autopsy case. J Clin Pathol. 2020. Epub 20200728. doi: 10.1136/jclinpath-2020-206879. PubMed PMID: 32723800.
97. Baldi BG, Fabro AT, Franco AC, Machado MHC, Prudente RA, Franco ET, et al. Clinical, radiological, and transbronchial biopsy findings in patients with long COVID-19: a case series. J Bras Pneumol. 2022;48(3):e20210438. Epub 20220429. doi: 10.36416/1806-3756/e20210438. PubMed PMID: 35508067; PubMed Central PMCID: PMC9064656.
98. Flaifel A, Kwok B, Ko J, Chang S, Smith D, Zhou F, et al. Pulmonary Pathology of End-Stage COVID-19 Disease in Explanted Lungs and Outcomes After Lung Transplantation. Am J Clin Pathol. 2022;157(6):908-26. doi: 10.1093/ajcp/aqab208. PubMed PMID: 34999755; PubMed Central PMCID: PMC8755396.
99. Konopka KE, Perry W, Huang T, Farver CF, Myers JL. Usual Interstitial Pneumonia is the Most Common Finding in Surgical Lung Biopsies from Patients with Persistent Interstitial Lung Disease Following Infection with SARS-CoV-2. EClinicalMedicine. 2021;42:101209. Epub 20211123. doi: 10.1016/j.eclinm.2021.101209. PubMed PMID: 34841234; PubMed Central PMCID: PMC8609167.
100. Li Y, Wu J, Wang S, Li X, Zhou J, Huang B, et al. Progression to fibrosing diffuse alveolar damage in a series of 30 minimally invasive autopsies with COVID-19

pneumonia in Wuhan, China. Histopathology. 2021;78(4):542-55. Epub 20201111. doi: 10.1111/his.14249. PubMed PMID: 32926596; PubMed Central PMCID: PMC8848295.
101. Kanne JP, Bai H, Bernheim A, Chung M, Haramati LB, Kallmes DF, et al. COVID-19 Imaging: What We Know Now and What Remains Unknown. Radiology. 2021;299(3):E262-E79. Epub 20210209. doi: 10.1148/radiol.2021204522. PubMed PMID: 33560192; PubMed Central PMCID: PMC7879709.
102. Lerum TV, Aaløkken TM, Brønstad E, Aarli B, Ikdahl E, Lund KMA, et al. Dyspnoea, lung function and CT findings 3 months after hospital admission for COVID-19. Eur Respir J. 2021;57(4). Epub 20210429. doi: 10.1183/13993003.03448-2020. PubMed PMID: 33303540; PubMed Central PMCID: PMC7736755.
103. Froidure A, Mahsouli A, Liistro G, De Greef J, Belkhir L, Gérard L, et al. Integrative respiratory follow-up of severe COVID-19 reveals common functional and lung imaging sequelae. Respir Med. 2021;181:106383. Epub 20210404. doi: 10.1016/j.rmed.2021.106383. PubMed PMID: 33839588; PubMed Central PMCID: PMC8019490.
104. Balbi M, Conti C, Imeri G, Caroli A, Surace A, Corsi A, et al. Post-discharge chest CT findings and pulmonary function tests in severe COVID-19 patients. Eur J Radiol. 2021;138:109676. Epub 20210320. doi: 10.1016/j.ejrad.2021.109676. PubMed PMID: 33798931; PubMed Central PMCID: PMC7980523.
105. van den Borst B, Peters JB, Brink M, Schoon Y, Bleeker-Rovers CP, Schers H, et al. Comprehensive Health Assessment 3 Months After Recovery From Acute Coronavirus Disease 2019 (COVID-19). Clin Infect Dis. 2021;73(5):e1089-e98. doi: 10.1093/cid/ciaa1750. PubMed PMID: 33220049; PubMed Central PMCID: PMC7717214.
106. Zhao YM, Shang YM, Song WB, Li QQ, Xie H, Xu QF, et al. Follow-up study of the pulmonary function and related physiological characteristics of COVID-19 survivors three months after recovery. EClinicalMedicine. 2020;25:100463. Epub 20200715. doi: 10.1016/j.eclinm.2020.100463. PubMed PMID: 32838236; PubMed Central PMCID: PMC7361108.
107. González J, Benítez ID, Carmona P, Santisteve S, Monge A, Moncusí-Moix A, et al. Pulmonary Function and Radiologic Features in Survivors of Critical COVID-19: A 3-Month Prospective Cohort. Chest. 2021;160(1):187-98. Epub 20210304. doi: 10.1016/j.chest.2021.02.062. PubMed PMID: 33676998; PubMed Central PMCID: PMC7930807.

Tables

Table 1. Acute, Subacute, and Chronic CT Findings of COVID-19 Pneumonia

Timeframe	Pattern	CT Findings
Acute (101)	Organizing pneumonia	Patchy peripheral and peribronchial ground glass opacity (GGO)and consolidation Perilobular thickening Small, round GGOs
	Diffuse alveolar damage	Diffuse GGO Admixed consolidation or crazy-paving Volume loss
Subacute (102-107)		GGO (66%) Reticular lesions (49%) “Fibrotic patterns” (21%) Traction bronchiectasis (21-26%)
Chronic (13-27)	Fibrosis	GGO and “fibrotic-like changes*” (21%) Bronchiectasis (10%,) Interlobular septal thickening (8%) Reticular opacity (6%) Consolidation (3%). *“Fibrotic-like changes” - architectural distortion with traction bronchiectasis - honeycombing - traction bronchiectasis/bronchiolectasis -volume loss

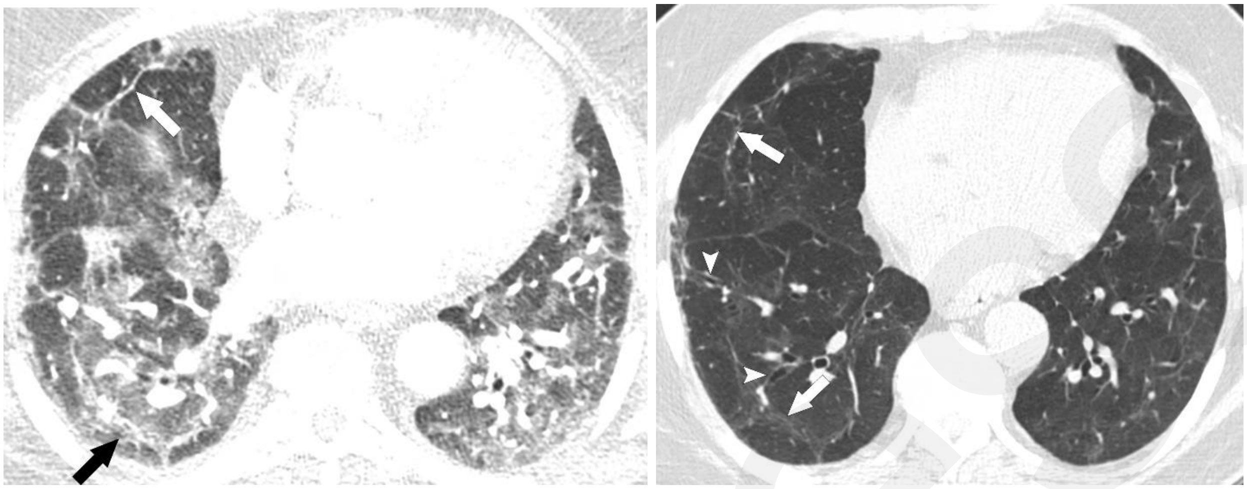
Table 2. Acute, Subacute, and Chronic Airway Findings of COVID-19 Pneumonia

Timeframe	Type	CT Findings
Acute / subacute (37-38, 45-46)		
	Large airway	Bronchial wall thickening
		Bronchial dilation (often reversible)
	Small airway	Air trapping
Chronic (19, 45-46, 48-50, 52-54)	Large airway	Peripheral, central, or diffuse bronchiectasis associated with residual opacities
		Anterior bronchiectasis with fibrosis and air cysts (adult respiratory distress syndrome survivors)
	Small airway	Mosaic attenuation (inspiration)
		Air trapping (expiration)
		Ventilation defects and abnormal gas diffusion (hyperpolarized 129Xe MRI)

Table 3. Acute Pulmonary Vascular Manifestations: COVID-19 Infection

Timeframe	Clinical Findings	Contributing Factors	Imaging Findings
Acute (61-65)	Elevated risk of pulmonary embolus and *in situ* thrombosis Multiorgan venous thromboembolism and microthrombosis, including in the pulmonary vascular bed Pulmonary vein thrombosis - case reports (78,79) Vaccination reduces the risk of COVID-19 associated pulmonary embolus during combined Delta and Omicron variant waves	Disease severity Patient immunity Possibly strain of SARS-CoV-2	Pulmonary embolism Possible relationship between venous thromboembolism risk and lung parenchymal CT severity score

Figures



A B

Figure 1. 63-year-old man with residual lung abnormalities from SARS-CoV-2 infection. **(A)** Contrast-enhanced axial CT image at presentation shows peripheral and peribronchial ground glass opacity and consolidation along with perilobular thickening (*arrows*). **(B)** Unenhanced axial CT image 1 year later shows patchy residual ground glass opacity, persistent perilobular thickening (*arrow*s), and mild bronchial dilation (*arrowheads*) in areas of ground glass opacity.

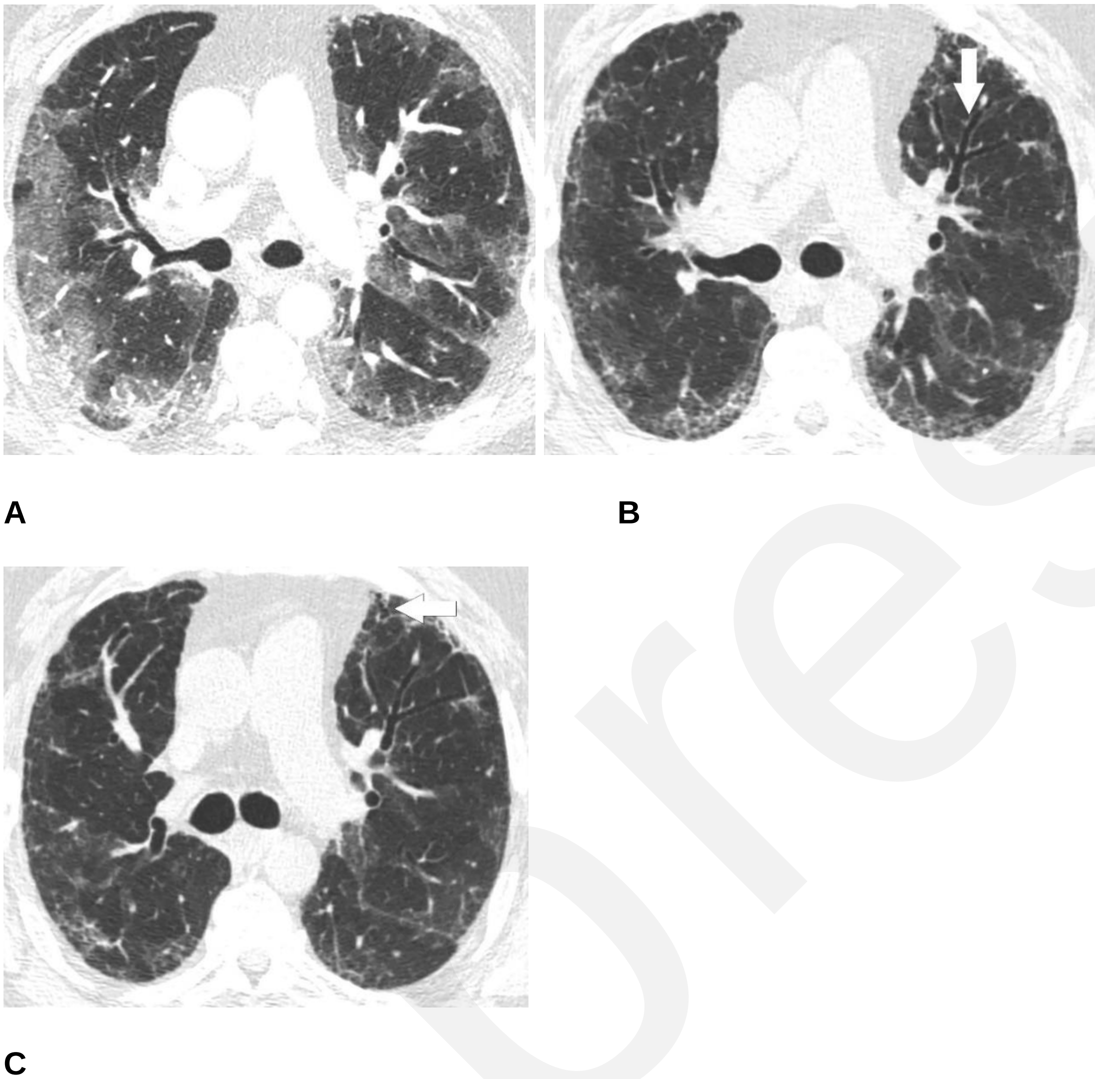
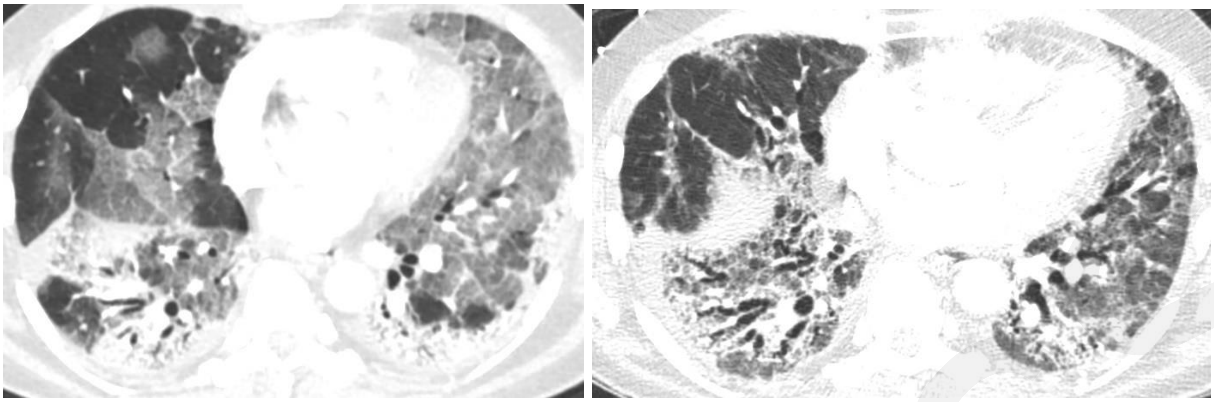


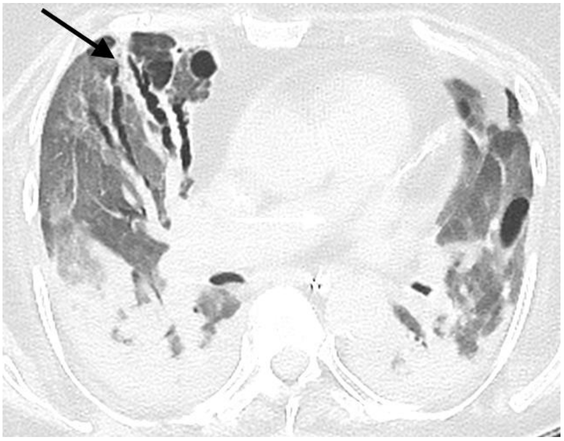
Figure 2. 57-year-old man with fibrosis resulting from SARS-CoV-2 infection. **(A)** Contrast-enhanced axial CT image at presentation shows peripheral predominant ground glass opacity with a small amount of consolidation. **(B)** Unenhanced axial CT image 3 months later shows marked clearing of ground glass opacity but development of reticulation and mild bronchial dilation (*arrow*). **(C)** Unenhanced axial CT image 6 months after infections shows further decrease of ground glass opacity and a lesser extent of reticulation. The area of bronchial dilation in the left upper lobe has resolved, although there is a small peripheral area of traction bronchiectasis (*arrow*).



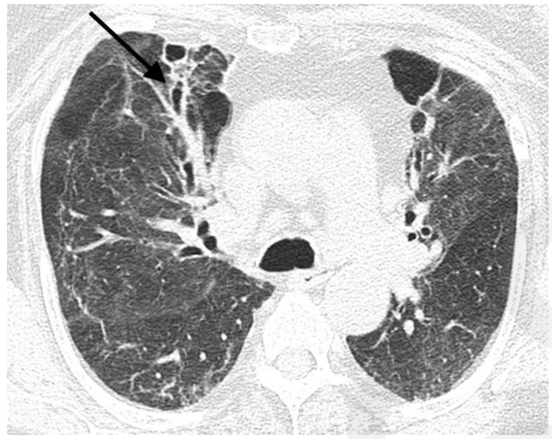
A **B**

Figure 3. 56-year-old man with fibrosis resulting from SARS-CoV-2 infection. **(A)** Contrast-enhanced axial CT image early during infection shows extensive ground glass opacity with posterior and peripheral predominant consolidation and some areas of crazy-paving. **(B)** Unenhanced axial CT image from 10 months later shows lower lobe predominant reticulation, traction bronchiectasis, and ground glass opacity with lower lobe volume loss.

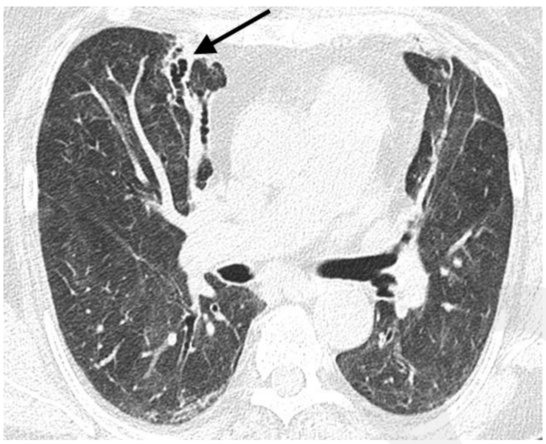
Figure 4. 74-year-old man with history of SARS-CoV-2 infection. Axial unenhanced axial CT image 5 months after acute infection shows bilateral residual peripheral ground glass opacity and bandlike opacities. Varicoid traction bronchiectasis and bronchiololectasis occurs within areas of reticulation and architectural distortion, in keeping with fibrosis (*arrows*).



A

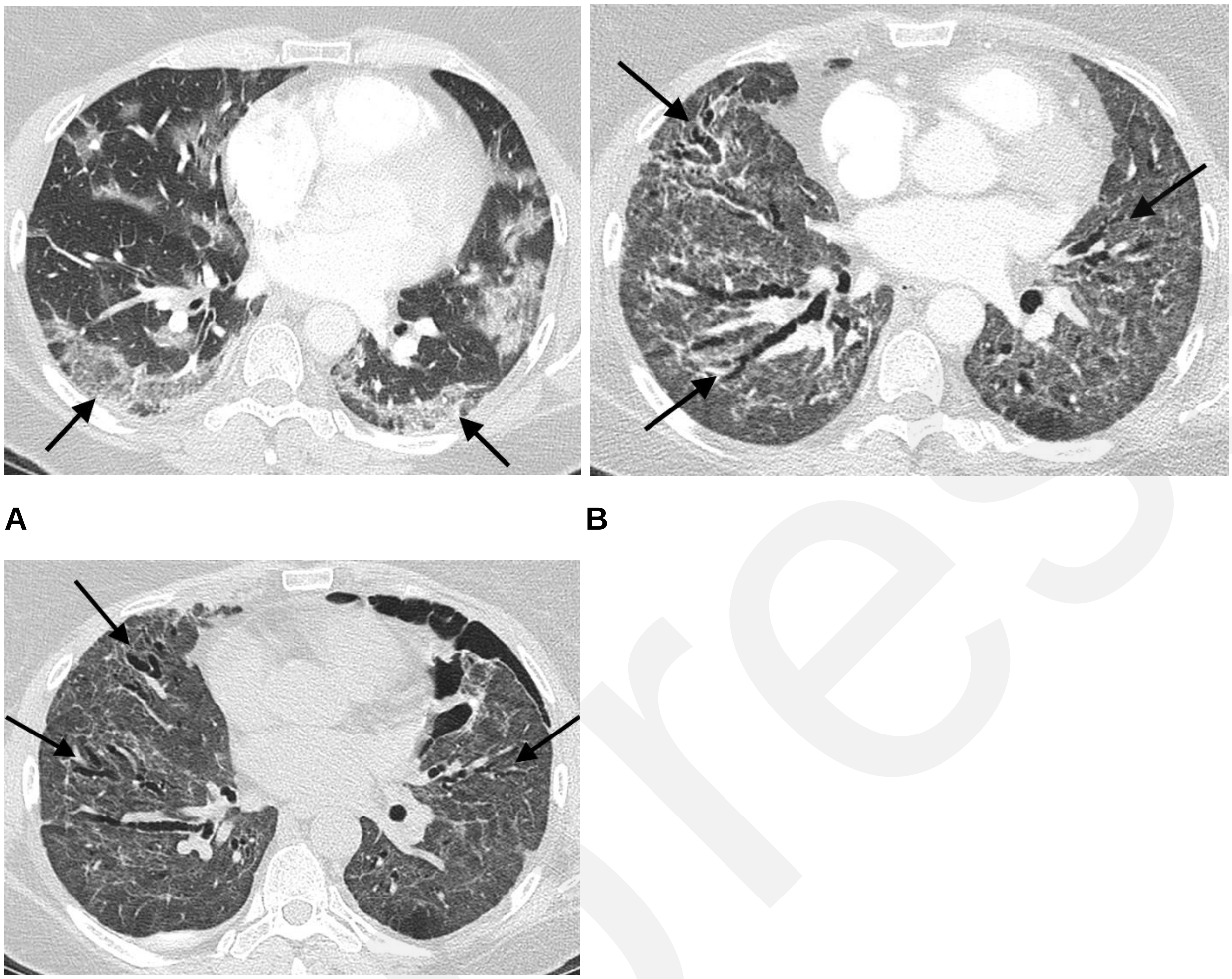


B



C

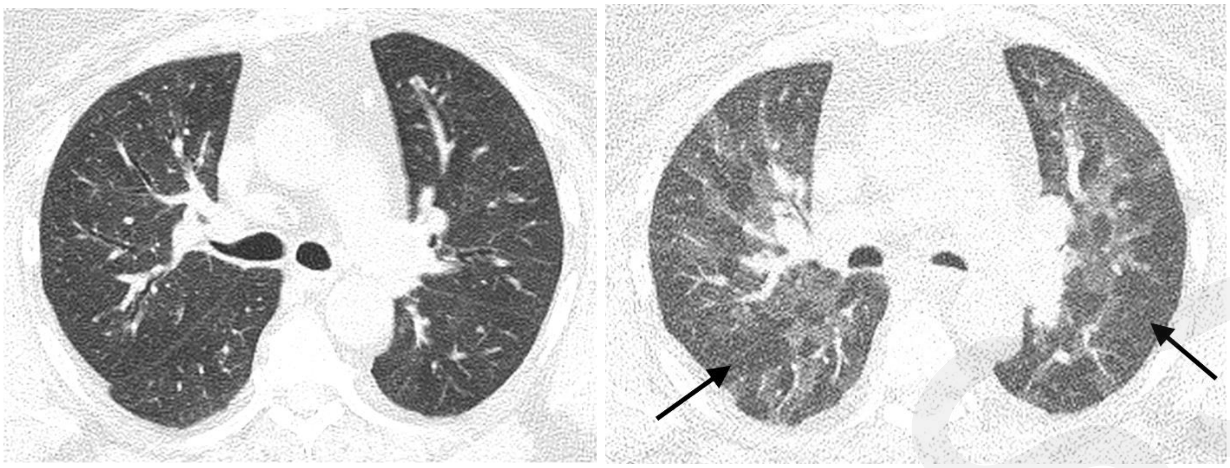
Figure 5. 77-year-old woman hospitalized with ARDS resulting from SARS-CoV-2 infection. **(A)** Unenhanced axial CT image during acute infection and mechanical ventilation shows typical findings of alveolar damage, with dependent consolidation and ground glass opacity throughout the remainder of the lungs. Varicoid bronchial dilation and an air cyst have developed within the anterior right lung (*arrow*). **(B, C)** Unenhanced axial CT images 10 months after infection show anterior predominant varicoid bronchiectasis (*arrows*), slightly decreased in severity and accompanied by reticulation and architectural distortion. A background of residual ground glass opacity, peripheral parenchymal bands, and reticulation is also present.



A B

C

Figure 6. 51-year-old woman with history of SARS-CoV-2 infection, noninvasive positive pressure ventilation, and chronic dyspnea requiring home oxygen therapy. **(A)** Contrast-enhanced axial CT image during acute infection shows bilateral ground glass opacity with a peripheral predominance (*arrows*). **(B)** Contrast-enhanced axial CT image after discharge, 2 months after presentation, shows diffuse ground glass opacity and architectural distortion with diffuse varicoid bronchial dilation (*arrows*). **(C)** Unenhanced axial CT image 6 months after presentation shows decrease in ground glass opacity but persistent diffuse varicoid bronchiectasis (*arrows*); a small left pneumothorax is also present.



A **B**

Figure 7. 58-year-old woman with history of SARS-CoV-2 infection, ongoing dyspnea after infection, and history of sleep apnea. **(A)** Unenhanced axial CT image at full inspiration performed 2 years after acute infection shows subtle diffuse mosaic attenuation. **(B)** Paired expiratory axial CT image shows extensive lobular and regional low attenuation indicative of air trapping (*arrows*).

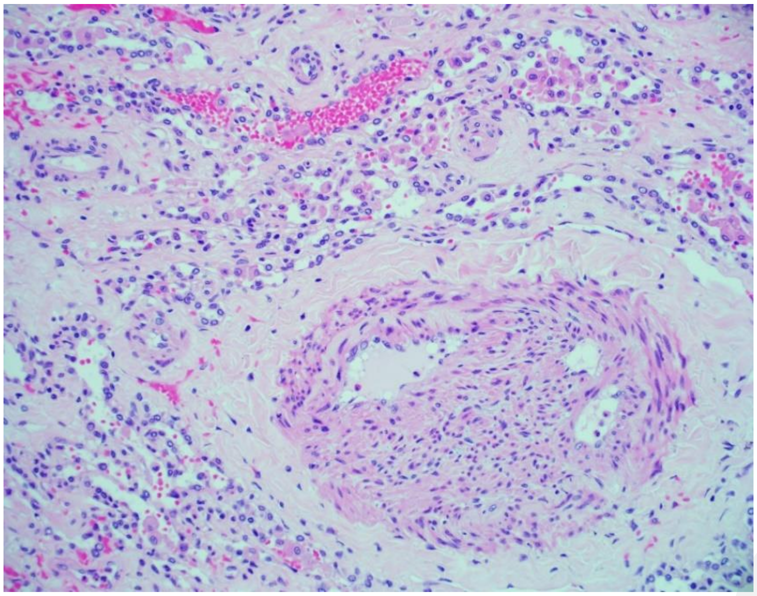


Figure 8. Recanalized pulmonary arteriole with neolumen formation. This finding was observed in an explanted lung 4 months after acute COVID-19. (Hematoxylin and eosin stain, 200X magnification)

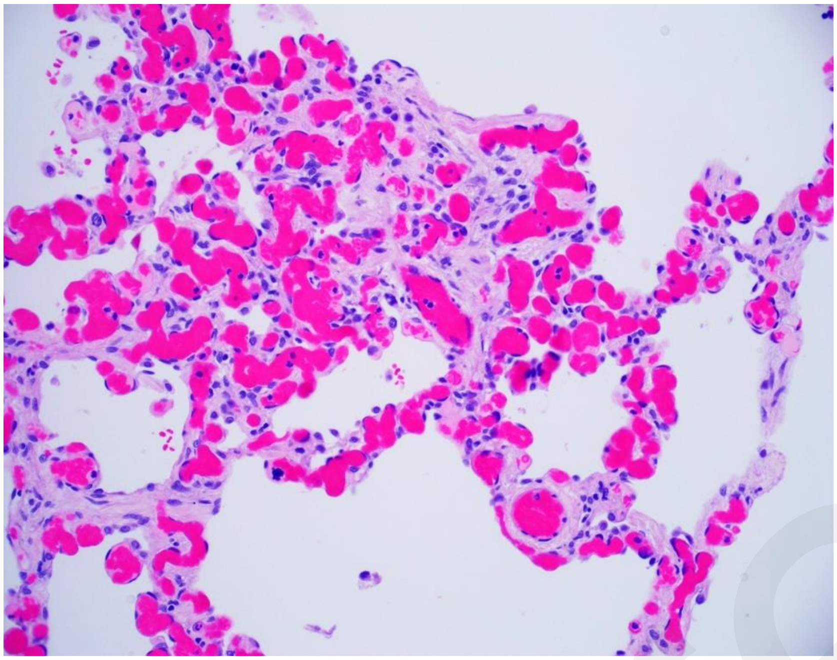


Figure 9. Alveolar septa showing vascular congestion and hemangiomatosis-like (VCHL) lesion. Notice the absence of acute lung injury, inflammation, and hyaline membrane formation. While originally described in the acute setting, this VCHL lesion was identified in an explanted lung approximately 4 months after acute COVID-19 pneumonia. (Hematoxylin and eosin stain, 200X magnification)

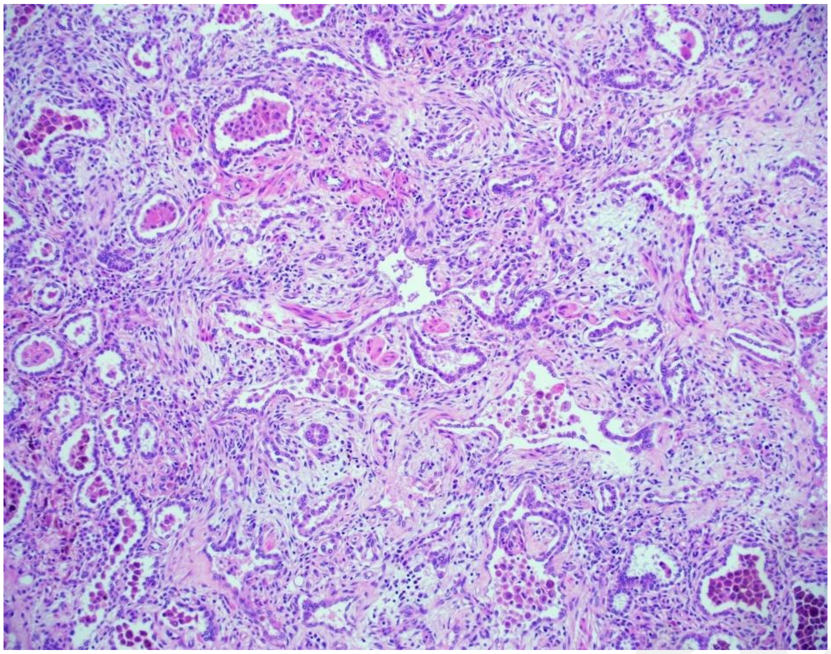


Figure 10. Section of pulmonary parenchyma showing organizing diffuse alveolar damage. There are residual alveolar spaces with marked increase in the interstitium by cellular fibroblastic proliferations. Some fibroblastic proliferations are also likely within alveoli. Type 2 pneumocyte hyperplasia is present. These findings were observed in an explanted lung approximately 6 months post-acute COVID-19 (Hematoxylin and eosin stain, 100X magnification)

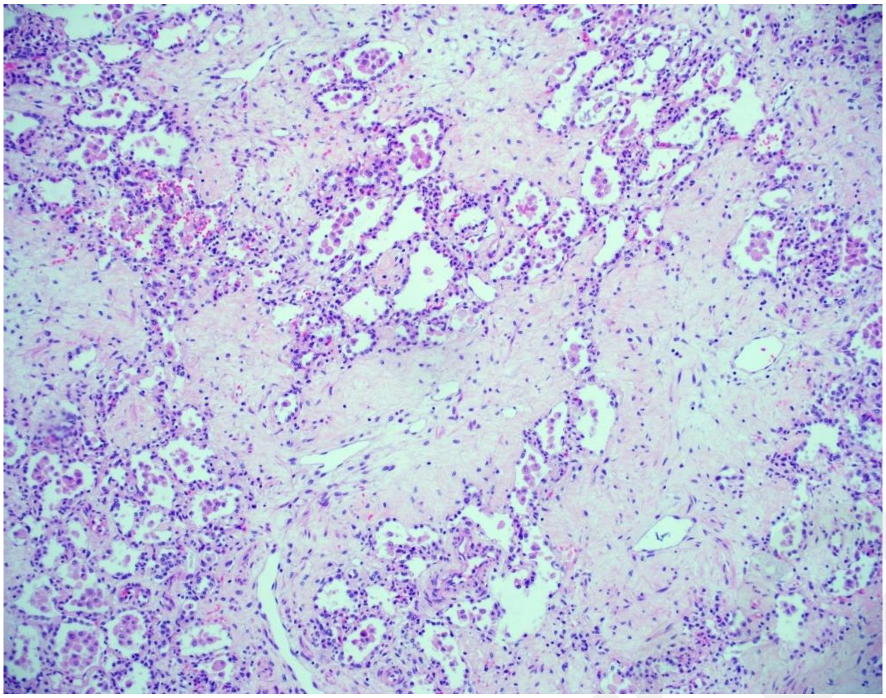


Figure 11. Diffuse pulmonary fibrosis in an explanted lung, 6 months following acute COVID-19. There is deposition of paucicellular, eosinophilic material within the pulmonary interstitium. Some residual alveolar spaces are present but appear compressed. These findings have been previously described in explanted lungs, and likely represent fibrotic phase of diffuse alveolar damage. (Hematoxylin and eosin stain, 100X magnification)

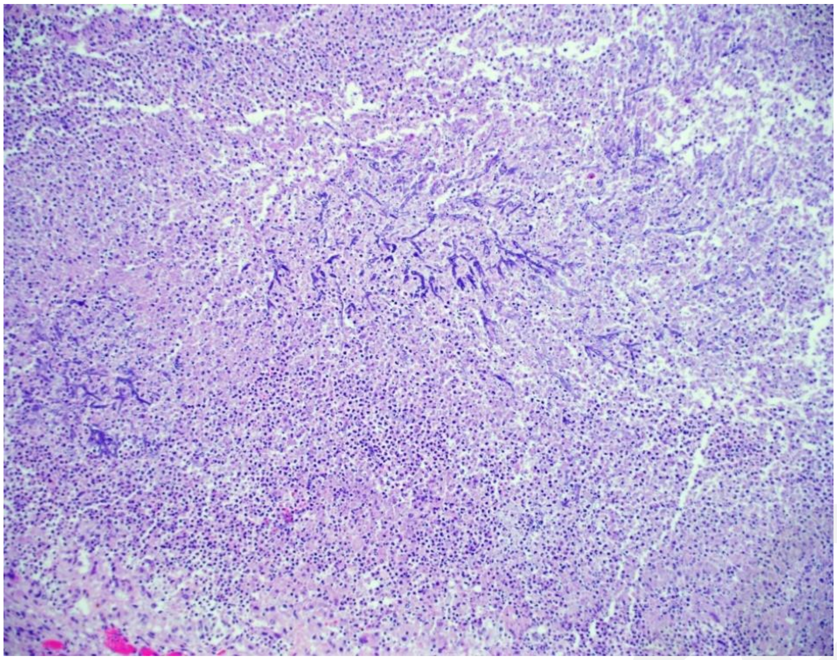


Figure 12. There are numerous fungal hyphae evident on hematoxylin and eosin stain with acute angle branching and septations. These fungal hyphae are favored to represent *Aspergillus*, but there no culture data was available. These fungi are seen in a background of marked neutrophilia, consistent with a necrotizing abscess. (Hematoxylin and eosin stain, 100X magnification)