Coronavirus Disease-2019 Pneumonia
Clinical Manifestations

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KEYWORDS

• COVID-19 • SARS-CoV-2 • Pneumonia • Clinical manifestations • CT chest

KEY POINTS

- Social risk factors for coronavirus disease-2019 (COVID-19) pneumonia such as race, ethnicity, income inequality, and living environment correlate with infection and severity of infection.
- Biological risk factors are numerous and highly correlate with cardiovascular disease and its risk factors.
- COVID-19 pneumonia has a broad presentation, ranging from mild illness to critical illness.
- Post-acute sequelae of severe acute respiratory syndrome coronavirus 2 has protean manifestations that can persist for months to over a year and is receiving increasing attention into its physiology and potential treatments.
- Imaging findings of pneumonia can be categorized as typical, indeterminate, and atypical and may differ according to vaccine status and viral variant.

INTRODUCTION

The global disease burden from coronavirus disease-2019 (COVID-19) infection has been unprecedented in recent history, with 619 million recorded cases and 6.55 million recorded deaths worldwide as of October 5, 2022[1] and with studies showing that these figures are likely underestimates.[2–4] Our understanding of its clinical manifestations has evolved due to increasing insight into risk factors, ability to triage, evolution of viral variants,[5,6] and imaging findings during and after acute infection.[7] Changes in the manifestations of COVID-19 pneumonia have also occurred, which has relevance for clinical care in ambulatory and hospital settings. Our approach to recognizing and managing COVID-19 will require ongoing study to adjust appropriately to the shifting disease burden that the global pandemic has created.

RISK FACTORS

Social Risk Factors for Infection and Severe Disease

Since the onset of the pandemic, racial and ethnic minorities—in particular the non-Hispanic black, Hispanic, and Native American communities—have experienced increased rates of infection, hospitalization, and mortality from severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Given that SARS-CoV-2 is spread through respiratory droplets, socioeconomic conditions have contributed to the disproportionate burden of COVID-19 in these underserved communities. Contributing factors that have been posited include a self-perpetuating system of income inequality, a disproportionate burden of underlying comorbidities, population-dense neighborhoods, family dense households, greater likelihood to work in public-facing occupations, less ability to

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stop working or to accept a furlough from work, and fewer health care resources in the neighborhoods of these communities.[8–13]

Income inequality has been strongly associated with increased case rate and mortality. One study examined COVID-19 cases and mortality and their association with the Gini index, a measure of income inequality, from January to April 2020 in a cohort of 577,414 cases and 23,424 deaths across 50 states. Multivariate regression with adjustment for multiple confounders (eg, older age, sex, race, health care resources, shelter-in-place order) revealed that a one-unit increase in the Gini index (ie, greater inequality of income) was associated with approximately a 27% increase in mortality.[14] This study did not adjust for comorbidities.

Race has been shown to correlate with increased risk of infection and hospitalization in multiple studies, even after adjustment for income level and other confounders. One study examined a cohort of 20,228 patients with SARS-CoV-2 in Houston in 2020, with covariate adjustment for age, sex, race, ethnicity, household income, residence population density, Charlson Comorbidity Index, hypertension, diabetes, and obesity. Higher likelihood of infection was found in non-Hispanic black individuals compared with non-Hispanic white (odds ratio [OR] 2.23, 95% confidence interval [CI] 1.90 to 2.60) and in Hispanic compared with non-Hispanic (OR 1.95, 95% CI 1.72 to 2.20).[8] A retrospective cohort study of 5698 patients from the University of Michigan from March to April 2020 and with an outcome update in July 2020 assessed the risk of hospitalization with statistical adjustment for multiple confounders, including a customized comorbidity score from seven known risk factors for disease severity: respiratory conditions, circulatory conditions, any cancer, type 2 diabetes, kidney disease, liver disease, and autoimmune disease.[15] Non-Hispanic black patients were more likely to be hospitalized for SARS-CoV-2 infection than non-Hispanic white patients (OR, 1.72, 95% CI 1.15 to 2.58, $P = .009$).

Vaccination Status

Reduced access to health care resources includes reduced access to vaccination, an issue that has persisted even after the widespread availability of vaccines for SARS-CoV-2. Large placebo-controlled trials have found a lower risk of asymptomatic, symptomatic, and severe COVID-19 with vaccinations,[16–18] and subsequent observational studies from national vaccine deployments have supported these findings.[19–21] In one study in the United Kingdom (UK) on vaccination of health care workers (23,324 participants from 104 sites), rates of effectiveness—as defined by not becoming infected—for the BNT162b2 vaccine were found to be 70% (95% CI 55% to 85%) at 21 days after the first dose and 85% (95% CI 74% to 96%) at 7 days after the second dose.[20] The study included asymptomatic and symptomatic infection and was conducted during a time of high prevalence of the Alpha variant. In a subsequent large study in England investigating effectiveness of various vaccine boosters against the Delta versus Omicron variant (204,154 individuals with Delta, 886,774 individuals with Omicron, 1,572,621 individuals with negative tests), vaccination effectiveness was uniformly higher for Delta than for Omicron.[20] **Table 1** shows the effectiveness of vaccine booster combinations.[22] One can see that booster vaccination with BNT162b2 or mRNA-1273 after either ChAdOx1 nCoV-19 or BNT162b2 primary vaccine courses improved effectiveness in a short time period (ie, 2 to 4 weeks) against Omicron. That effectiveness waned rapidly, however, dropping to as low as 39.6% to 45.7% at 10 or more weeks.

Worse clinical outcomes are much more likely to occur in persons with no vaccination versus booster vaccine and in persons with primary vaccination versus booster vaccine. In a study in Northern California including 118,078 persons that adjusted for confounders such as age, sex, comorbid burden, prior infection, and receipt of prior treatment of SARS-CoV-2, risk of hospitalization was higher in persons who were unvaccinated (adjusted hazard ratio [aHR] 8.34, 95% CI 7.25 to 9.60) and who had the primary vaccine course (aHR 1.72, 95% CI 1.49 to 1.97) compared with those who received the primary vaccine course plus a booster.[23]

Biological Risk Factors for Severe Disease

Early in the pandemic, patients with advanced age and certain underlying comorbidities were noted to be at higher risk of admission and severe disease. In an analysis of 208 acute care hospitals in England, Wales, and Scotland from February to April 2020, the median age of admission was 73 years (interquartile range [IQR] 58 to 82), and men constituted 60% of admissions ($n = 12,068$, from 18,525 total).[24] Comorbid burden was common, with only 23% of patients having no major comorbidity. Cardiovascular disease and its risk factors were common in patients: cardiac disease 31%; diabetes 21%; and chronic kidney disease 16%. Non-asthmatic chronic pulmonary disease was noted in 18% of patients. These findings were similar to data on adult hospitalization in 14 states in the United States in March 2020,

Table 1
Effectiveness of coronavirus disease-2019 vaccine series with subsequent combination boosters

Primary Course Vaccine[a]	Booster Vaccine	Effectiveness at 2 to 4 wk (%, 95% CI)	Effectiveness at 5 to 9 wk (%, 95% CI)	Effectiveness at 10 or More Weeks (%, 95% CI)
ChAdOx1 nCoV-19	BNT162b2	62.4 (61.8 to 63.0)	Not measured	39.6 (38.0 to 41.1)
BNT162b2	BNT162b2	67.2 (66.5 to 67.8)	Not measured	45.7 (44.7 to 46.7)
ChAdOx1 nCoV-19	mRNA-1273	70.1 (69.5 to 70.7)	60.9 (59.7 to 62.1)	Not measured
BNT162b2	mRNA-1273	73.9 (73.1 to 74.6)	64.4 (62.6 to 66.1)	Not measured

[a] Single vaccination for ChAdOx1 nCoV-19 and two vaccinations for BNT162b2.
Adapted from Andrews N, Stowe J, Kirsebom F, et al. Covid-19 Vaccine Effectiveness against the Omicron (B.1.1.529) Variant. N Engl J Med. 2022;386(16):1532-1546.

where 89.3% of patients had at least one underlying condition: 50% hypertension; 48% obesity; 35% chronic lung disease; 28% diabetes; 28% cardiovascular disease; and 13% renal disease.[25]

Ongoing caution is important for individuals with certain risk factors even after vaccination. In a prospective, nested, case-control study from the UK using self-reported data via phone from 6,030 adults with the first vaccine dose and 2370 adults with the second vaccine dose, infection 14 days or more after the first dose was found to be associated with frailty in individuals greater than or equal to 60 years of age (OR 1.93, 95% CI 1.50 to 2.48, $P < .0001$).[26] As before the era of widespread vaccination, residence in economically-deprived areas was associated with a greater risk of infection (OR 1.11, 95% CI 1.01 to 1.23, $P = .03$), and not being obese as defined by body mass index < 30 was associated with less risk of infection (OR 0.84, 95% CI 0.75 to 0.94, $P = .0030$). Of note, the association of increased infection risk persisted even after adjustment for compliance with preventative measures such as mask wearing. The above findings suggest than greater resources for re-vaccination, booster vaccination, and screening may be warranted in care facilities for individuals with high frailty (eg, long-term care homes) and in lower income neighborhoods.

Laboratory Abnormalities Associated with Severe Disease

There are numerous laboratory abnormalities that have been found to associate with severe disease. Leukocytosis has been associated with disease progression and severity,[27–29] and studies have found that lymphopenia is associated with disease severity and with worse outcomes.[29–33] Thrombocytopenia has been routinely observed in patients with COVID-19, with lower platelets manifesting in severe and critical illness[34] and being associated with higher mortality.[35] Additionally, worse outcomes have been observed in patients with elevations in numerous, routinely available inflammatory markers: D-dimer, C-reactive protein, lactate dehydrogenase, and ferritin.[36,37] Specific cytokines have also been implicated with decreased patient survival—in particular interleukin 6, 8 and Tumor-Necrosis-Factor-alpha (TNF-alpha).[38] The presence of viral RNA in the blood has been associated with increased end-organ damage, including the lung, and mortality.[39,40] Higher plasma nucleocapsid antigen level has also been found to be strongly associated with the need for noninvasive positive pressure ventilation or supplemental oxygen by high-flow nasal cannula.[41]

CLINICAL COURSE

Spectrum of Disease

The spectrum of presentation for SARS-CoV-2 infection is broad. The National Institutes of Health (NIH) definitions for infection severity are detailed in **Table 2**.[42]

Presymptomatic infection and mild to moderate illness are seen in the outpatient setting. A standard approach for outpatients is to note the date of symptom onset and the date of dyspnea onset, if any. This addresses the difficulty of measuring the incubation period, which has median estimates of approximately 3 days for the Omicron variant[6,43] to 4 to 5 days for older variants.[44] Patients who progress from mild disease to dyspnea have been observed to do so in the range of 5 to 8 days after the onset of mild illness.[45,46] In a prospective cohort study in Baltimore of 118 outpatients infected with SARS-CoV-2 and followed from April to June 2020, most of the patients (63.7%) had no symptoms or mild symptoms in the first week of illness.[47] Of those who had symptoms, fatigue or weakness were the most common (65.7%). This was followed by cough (58.8%), headache (45.6%), chills (38.2%), and anosmia (27.9%). These individuals reported returning to

Table 2
National Institutes of Health classification of infection with severe acute respiratory syndrome coronavirus 2[42]

Infection Severity	Criteria
Presymptomatic infection	Positive nucleic acid amplification test or antigen test but no symptoms.
Mild illness	Fever, cough, or sore throat but no dyspnea or abnormal imaging.
Moderate illness	Evidence of lower respiratory disease by auscultation of lungs or imaging and oxygen saturation $\geq$ 94% on room air at sea level.
Severe illness	Oxygen saturation $\leq$ 94% on room air at sea level, a ratio of arterial partial pressure of oxygen to fraction of inspired oxygen $\leq$ 300 mm Hg, respiratory frequency > 30 per minute, or lung opacities on imaging that have increased by 50% or more in 24 to 48 h.
Critical illness	Respiratory failure, shock due to sepsis, with or without non-pulmonary end-organ dysfunction.

their baseline health at a median of 20 days (IQR 13 to 38) after the onset of symptoms. After 28 to 99 days from symptom onset, 83.3% of patients reported returning to their baseline health. A total of 7.6% required hospitalization. In contrast, a large Cochrane review of 42 prospective studies with 52,608 participants found that most symptoms have low diagnostic accuracy on presentation, although anosmia and ageusia can provide unique triggers for screening and cough can warrant additional testing.[48] In this review the summary likelihood ratio (LR) of anosmia as a presenting symptom to be associated with SARS-CoV-2 infection was 4.55 (95% CI 3.46 to 5.9); for ageusia 3.14 (95% CI 1.79 to 5.51); for cough 1.14 (95% CI 1.04 to 1.25); for fever 1.52 (95% CI 1.10 to 2.10); and for sore throat 0.814 (95% CI 0.714 to 0.929). The authors point out that this latter LR suggests sore throat increases the odds of an alternative infectious process, implying that isolated upper respiratory symptoms such as sore throat or rhinorrhea do not support polymerase chain reaction testing for SARS-CoV-2.

Patients with severe illness require admission, and common presenting symptoms in these individuals are fatigue, cough, fever, and hypoxemia. In a retrospective study from Germany of 57 patients admitted to the medicine ward from February to April 2020, the median age was 72 years (IQR 60 to 81), with 23% women.[49] Fifty-six patients had at least 1 comorbid condition, and all patients required supplemental oxygen (median 2 L/min, IQR 2 to 4) to maintain oxygen saturation levels $\geq$ 94%. Fever was the most common presenting symptom (68%), followed by cough (60%), dyspnea (44%), and fatigue (37%). A majority (77%) had bilateral opacities on initial imaging. Median fever lasted 7 days (IQR 2 to 11), hospitalization 12 days (IQR 7 to 20), and oxygen supplementation 8 days (IQR 5 to 13). In this study and in numerous reports since the beginning of the pandemic, hypoxemia without dyspnea has been described. Some authors posit that the observation may be due to known physiologic principles such as isocapnic hypoxia having a nonlinear ventilatory response in which minute ventilation increases markedly only after arterial oxygen drops below a specific threshold (eg, Pa_{O_2} 60 mm Hg).[50–52] It is notable that a study conducted years before this pandemic by Moosavi and colleagues[53] also found that dyspnea exhibits the same response mechanism, with a sharp increase in reported "air hunger" ratings seen primarily in isocapnic patients with Pa_{O_2} less than 60 mm Hg.

Critical illness also manifests with profound hypoxemia but has, in contrast to severe illness, the distinguishing feature of acute respiratory failure.[24,54] Presenting symptoms of these patients are similar to those who do not progress to critical disease (eg, fever, cough).[24,55,56] In patients who develop Acute Respiratory Distress Syndrome (ARDS) after infection with SARS-CoV02, the median time from confirmation of infection to the onset of dyspnea has been reported as 6.5 days.[57,58] The median time from the onset of dyspnea to ARDS has been reported as 2.5 days. Complications such as pneumothorax and barotrauma in patients with ARDS secondary to COVID-19 pneumonia may be higher compared with other patients with ARDS.[59,60] Mechanical ventilation for ARDS in COVID-19 may be an independent risk factor for death compared with ARDS

patients who experience barotrauma from noninvasive positive pressure ventilation.[61,62] In a small study comparing ARDS secondary to COVID-19 (n = 27) to non-COVID-19 ARDS (other viral n = 14, bacterial n = 21, culture-negative pneumonia n = 30), time to ventilator liberation was longer for patients with COVID-19 after adjustment for age, sex, and nursing home residence (aHR 0.48, 95% CI 0.24 to 0.98, $P < .05$).[63] No significant difference was found in 2-month mortality between the groups (aHR 0.71, 95% CI 0.33 to 1.56; $P = .39$). Similarly, no difference in mortality at 28 days was found in a second study comparing 130 patients with COVID-19 ARDS to 382 patients with non-COVID-19 ARDS (adjusted risk ratio 1.01, 95% CI 0.72 to 1.42).[64]

Post-Acute Sequelae of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2)

Recovery from acute COVID-19 ranges along a spectrum, with no clear consensus on what constitutes Post-Acute Sequelae of SARS-CoV-2 (PASC). A clinical case definition by the World Health Organization makes the distinction that acute COVID-19 lasts up to 4 weeks after the onset of illness; whereas PASC can develop during or after COVID-19 and must continue at least 3 months after the onset of illness.[65] Common symptoms include fatigue, cognitive impairment, and dyspnea. In a study from Germany of 96 patients with symptom onset between February 2020 and April 2020 and who had follow-up visits at 5, 9, and 12 months, the most frequent symptoms at 5 months were reduced exertional ability (53.1%), fatigue (41.7%), insomnia (32.3%), cognitive impairment (31.3%) and dyspnea (27.1%).[66] From 5 to 12 months, reported fatigue increased from 41.7% to 53.1% (P = .043); dyspnea increased from 27.1% to 37.5% (P = .041). All other symptoms did not change significantly. This and a second prospective study of 968 patients in France found that 80% to 85% of patients still reported symptoms 1 year after symptom onset.[67] Research into the characteristics of PASC and potential treatments is ongoing.

Associated Infections

Bacterial infections in patients with COVID-19 pneumonia are uncommon and can be distinguished between co-infection and superinfection. The former is diagnosed at the time of COVID-19 pneumonia diagnosis and is presumably acquired in the community. The latter is diagnosed during the period of management for COVID-19 pneumonia. One study in Spain in 2020 reported a co-infection rate of 3.1%, primarily with *Streptococcus pneumoniae* and *Staphylococcus aureus*, and a superinfection rate of 4.7%, primarily with *Pseudomonas aeruginosa* and *Escherichia coli*.[68] A meta-analysis including 2390 patients found higher rates of bacterial co-infections (8%, 95% CI 5% to 11%) and bacterial superinfections (20%, 95% CI 13% to 28%).[69] Significant rates of viral and fungal secondary infections were also noted: viral co-infections, 10% (95% CI 6% to 14%); viral superinfections, 4% (95% CI 0% to 10%); fungal co-infections, 4% (95% CI 2% to 7%); and fungal superinfections, 8% (95% CI 4% to 13%). The most common bacterial pathogens for co-infection were *Klebsiella pneumoniae* (9.9% of all co-infections), *S pneumoniae* (8.2%), and *S aureus* (7.7%). The most common bacterial pathogens for superinfection were *Acinetobacter spp.* (22.0%), *Pseudomonas* (10.8%), and *E coli* (6.9%).[69] Aspergillus was found in 6.7% of co-infections and 13.5% of superinfections.

RADIOGRAPHIC FINDINGS

Chest X-ray can be normal in early or mild disease, and when radiographic findings develop, they typically reveal bilateral opacities that are predominant in the lower lobes.[70] Pulmonary opacities can become more extensive and confluent thereafter, followed by the consolidation seen in acute lung injury.[71] Most patients will experience resolution, but some can progress to a more structured parenchymal injury manifesting as reticular opacities and associated fibrosis.[72] **Fig. 1** illustrates typical chest x-ray findings during initial stages of infection with COVID-19 pneumonia and the evolution to fibrotic changes over time.

Early in the pandemic, temporal stages of CT findings in COVID-19 pneumonia were proposed and included ultra-early, early, rapid progression, consolidation, and dissipation.[73] The ultra-early stage can occur within 2 weeks of exposure and can present with no or scant ground glass opacities (GGOs) on imaging. Symptomatic presentation occurs during the early phase, which may include single or multiple GGOs with interlobular septal thickening. Rapid progression is expected 3 to 7 days after symptomatic presentation and manifests with consolidations and air bronchograms. The consolidation phase occurs 7 to 14 days after symptomatic presentation, when the size and density of consolidations decrease. Dissipation may occur thereafter. It can include reticulations with opacities, thickening of the bronchial wall, and interlobular septal thickening.

Typical chest CT abnormalities are consistent with viral pneumonia, with one large review finding

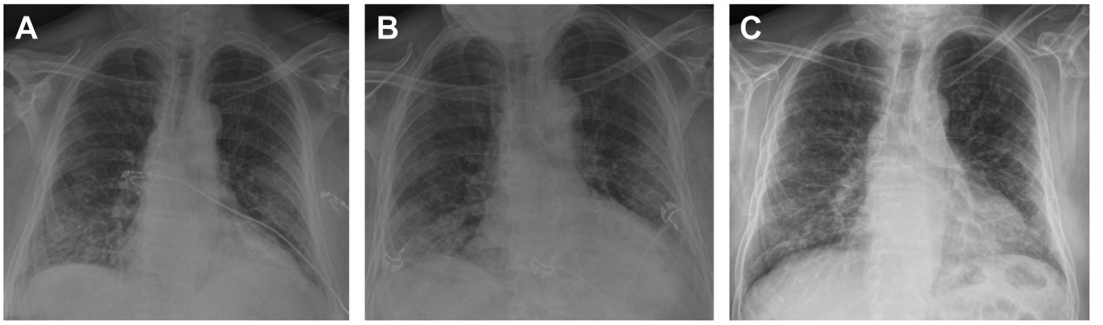

Fig. 1. Serial chest radiographs of a 62-year-old gentleman with a history of essential hypertension with COVID-19 pneumonia and requiring hospital admission and oxygen support by non-rebreather mask. He received remdesivir, dexamethasone, ceftriaxone, and azithromycin in hospital and was discharged on home oxygen. (*A*) Day of first positive SARS-CoV-2 polymerase chain reaction test, taken 9 days after onset of symptoms. Bilateral opacities on the left greater than the right. Air bronchograms and bronchial wall thickening is noted in the right lower lobe. (*B*) Two days after positive test. Slight worsening of bilateral opacities is seen; (*C*) Eleven months after infection. Bilateral opacities and prominent interstitial markings are consistent with fibrotic lung disease, likely a sequelae of lung injury from acute infection.

GGOs to be the most prominent feature (83%), followed by GGOs with mixed consolidation (58%), pleural thickening (52%), and interlobular septal thickening (48%).[7] Criteria have been proposed by the Radiological Society of North America (RSNA) to categorize CT chest findings as *typical*, *indeterminate*, and *atypical*.[74] *Typical* is defined as either multifocal rounded GGOs or peripheral bilateral GGOs with or without consolidation or the superimposed interlobular septal lines that constitute "crazy paving." (Fig. 2) A later stage of typical pneumonia is defined as having reverse halo sign or other signs of organizing pneumonia. *Indeterminate* is defined as absence of these typical features with the addition of GGOs that are non-rounded, non-peripheral and either diffuse, perihilar, unilateral, or simply lacking a specific distribution. *Atypical* is defined as lacking the features of typical and indeterminate and having lobar or segmental consolidation, centrilobular nodules, or lung cavitation. These acute insults can evolve into a chronic phase of inflammation, resulting in subpleural reticulation and bronchiectasis (Fig. 3).

Vaccinations attenuate the radiographic presentations of COVID-19, consistent with the impact of vaccinations on disease severity. In a multicenter Korean study, infected patients were divided into groups of unvaccinated, partially vaccinated, and fully vaccinated and had their clinical metrics and radiographic features analyzed for comparative differences.[75] Vaccine status (fully vaccinated vs unvaccinated) was associated with less risk of needing supplemental oxygen (OR 0.24, 95% CI 0.09 to 0.64, $P = .005$) or intensive care unit (ICU) admission (OR 0.08, 95% CI 0.09 to 0.78, $P = .02$). Of the 761 patients, 412 received chest CT and 75% of these were diagnosed with pneumonia. The percentage of patients with negative

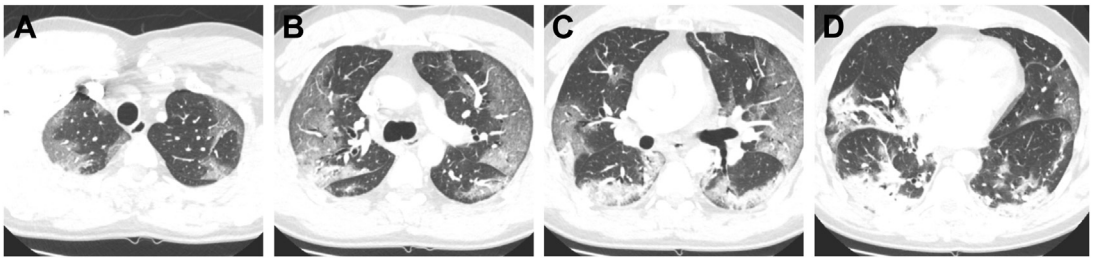

Fig. 2. Axial cuts of a CT angiogram of the chest of a 50-year old gentleman with a history of hyperparathyroidism with typical COVID-19 pneumonia per Radiological Society of North America criteria, taken 1 day after first positive polymerase chain reaction for SARS-CoV-2. The patient required ICU admission and oxygen support by high flow nasal cannula. He was discharged on home oxygen. (*A*) Bilateral, peripheral GGOs in the left upper lobe; (*B*) bilateral GGOs with mild consolidations and mild traction bronchiectasis at the level of the carina; (*C*) Increasing consolidative opacities intermixed with GGOs and more severe bronchiectasis; and (*D*) Bibasilar, posterior, peripheral consolidative opacities with peripheral GGOs.

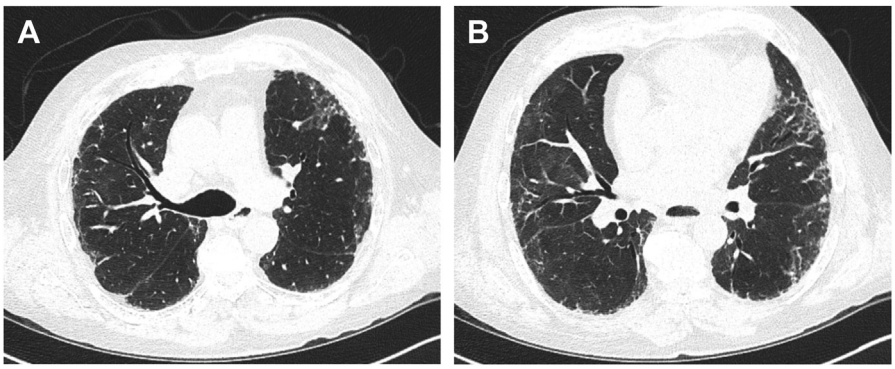

Fig. 3. CT chest scan 5 months after COVID-19 pneumonia in the same patient presented in Fig. 1. (*A*) Subpleural peripheral reticulations seen in the bilateral upper lobes. Traction bronchiectasis in left upper lobe takeoff; (*B*) Peripheral GGOs with reticulation in bilateral lower lobes. These findings seem to represent fibrotic lung disease.

CT chest significantly increased with vaccine status—22% of unvaccinated compared with 59% of fully vaccinated. Most of the patients in each vaccine group had typical CT chest findings as defined by RSNA criteria, but these percentages decreased from unvaccinated (72%) to partially vaccinated (60%) to fully vaccinated (56%). This trend was largely due to a greater percentage of fully vaccinated persons having atypical CT chest findings (11%) compared with partially vaccinated (2%) and unvaccinated (3%).

A subsequent study in Korea examined CT chest findings for COVID-19 pneumonia in patients during the Delta wave ($n = 88$) compared with the Omicron wave ($n = 88$).[76] After adjustment for the confounders of age, comorbid burden, vaccination status, and infection duration, patients with Omicron were found to have a less typical CT appearance for COVID-19 pneumonia per RSNA criteria (OR 0.34, 95% CI 0.16 to 0.74, $P = .006$) and more peribronchovascular involvement than patients with Delta (OR 9.2, 95% CI 2.9 to 29, $P < .001$). By using a neural network algorithm, the authors found that pulmonary vascular volume in vessels 5 mm or less in diameter (ie, vessels in the periphery of the lung) was greater for patients with Omicron than patients with Delta (3.8, 95% CI 0.92 to 6.8, $P = .01$). Together, these findings reinforced prior studies that Omicron replicates more predominantly in the bronchi than in the lung parenchyma and that the differing physiologic mechanisms of the variant resulted in distinct radiographic findings.[77] The higher volume of peripheral pulmonary vascular volume in patients with Omicron was consistent with it causing less severe pneumonia than Delta, given that lower peripheral vascular volume (ie, blood vessel volume less than 5 mm in diameter) has been found to associate with worse outcomes for COVID-19 pneumonia.[78] The study was significant in its implication that emerging variants of concern may produce radiographic findings that are increasingly atypical and therefore at risk of delayed detection.

LESSONS LEARNED

COVID-19 has posed an unprecedented challenge to our diagnostic and prognostic approaches of viral respiratory illness. Since the beginning of the pandemic in late 2019, we have acquired knowledge in the protean manifestations of the disease and in the social and biological risk factors for infection and severe disease. This includes elucidation of critical social and biological determinants of health and codification of disease severity and imaging findings. A commitment to continuing and advancing such research will be crucial for ameliorating the impact of newer viral variants on individual and population health and for preparing for future pandemics.

As viral variants evolve and vaccines continue to be developed, we will be presented with new challenges in identifying and managing upper and lower respiratory tract infection with COVID-19. Phenomena such as post-acute sequelae of COVID-19 have already become prominent, and longer-term morbidity from physiologic damage caused by acute disease will continue to accumulate. The international coordination shown by SARS-CoV-2 vaccine development offers a model for cooperation and scientific knowledge dissemination in these crucial domains. In a similar collaborative vein, the US Centers for Disease Control and Prevention (CDC) has established a Center for Forecasting and Outbreak Analytics in April 2022 to integrate analysts from previously siloed fields of computer science, mathematics, physics, and epidemiology and to allow for a more preemptive approach to future pandemics.[79] To ensure

greater equity in vaccine distribution, the CDC has partnered with the Health Resources & Services Administration (HRSA) to deliver vaccines directly to HRSA-funded health centers. These centers serve 30 million individuals in the United States, 93% of them are below 200% of the federal poverty level, and 63% of them identify as racial or ethnic minorities.[80] As societies have reopened and the virus has become endemic, we should continue to pay heed to the suffering and harm that could have been mitigated by this pandemic and apply these difficult lessons to such committed advancement of improved pathways for clinical care.

CLINICS CARE POINTS

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- Biological risk factors are numerous and highly correlate with cardiovascular disease and its risk factors.
- COVID-19 pneumonia has a broad presentation, ranging from mild illness to critical illness.
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