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Variants and Vaccination in COVID-19: New Complexities and Challenges for Radiology Research and Practice

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See also the article by Lee et al.

The ongoing COVID-19 pandemic has dramatically changed in the almost 3 years since SARS-CoV-2 emerged in late 2019. Vaccination and acquired immunity have contributed to a decrease in the number of severe infections, and antiviral therapies and better supportive therapies have led to improved outcomes. However, the path has been and will remain circuitous, influenced by vaccination rates and effectiveness, and progressive waves of dominant viral variants, each with different abilities to infect and cause disease, and different susceptibilities to existing vaccines. In this edition of *Radiology*, [the authors] provide not just a large multicenter study of associations of vaccination status, viral variants, and imaging appearance and severity in COVID-19, but also give a glimpse into the future of research and practice that must incorporate the complex interactions between evolving viral and host characteristics.

[The authors] analyzed a population of 2180 hospitalized patients with COVID-19 from 3 centers, using semi-quantitative chest radiograph and CT scores to assess associations between imaging severity of pneumonia, vaccination status, and SARS-CoV-2 variant type. The authors chose periods during which variants were dominant in the region, comparing the periods August - December, 2021 (Delta dominant) and February - March 2022 (Omicron dominant). Vaccination was stratified by unvaccinated, partially vaccinated, fully vaccinated, and boosted statuses. In a multivariable analysis, the authors controlled for an overall higher severity of illness in hospitalized patients for the Omicron-predominant period due to changing public health measures that resulted in home treatment of mild to moderate infection. Patients during the Omicron-dominant period were more likely to have imaging negative for pneumonia and lower CXR and CT pneumonia severity scores. Vaccination was strongly associated with lower severity of PNA at imaging, and better clinical outcomes, with least risk of pneumonia in boosted patients. In multivariate analysis, Omicron was associated with better outcomes than patients infected with Delta. Further, of patients with imaging evidence of pneumonia at CT, only 42% of patients with Omicron had a "typical" CT appearance by the RSNA expert guideline, compared with 76% of the Delta variant group.

[The authors'] finding of lower radiologic severity of COVID-19 pneumonia in vaccinated individuals is not surprising. Although COVID-19 vaccines provide some short-term protection against infection via neutralizing antibodies, the primary goal of vaccination has been to prevent severe clinical consequences, including death. Discounting other confounding factors, more severe pneumonia should be associated with greater severity at radiography and CT, and many previous studies have found correlations between imaging severity and clinical endpoints such as hospitalization, ICU admission, mechanical ventilation, and death (1). Recent studies have also shown differences in imaging

appearance and severity between breakthrough infections in vaccinated individuals and infections in the unvaccinated, even comparing different vaccine types (2). Differences in radiological severity of pneumonia between SARS-CoV-2 variants have also been documented previously, including comparisons of the Alpha strain to Omicron (3), and Omicron to Delta (4).

[The authors'] study successfully combines these themes, analyzing associations between variants and vaccination status, comorbidities, and patient demographics on imaging severity and appearance, and clinical outcomes. Previous studies have been largely single-center, with smaller patient populations, and have not fully addressed these variables together. The authors provide a robust proof that both vaccination status (none, partial, full, boosted) and time from vaccination correlate with likelihood of pneumonia at imaging. The results confirm the results of previous studies, and provide a model for future research.

[The authors] show lower proportions of "typical" appearances in those infected with an Omicron variant, concordant with recent work showing that the diagnostic accuracy of RSNA guidelines for COVID-19 reporting has fallen significantly with the rise of vaccination and viral mutation (5). As the authors point out, this is likely at least in part due to the presence of infections other than SARS-CoV-2, either as the primary driver of imaging severity and appearance, or as an important co-infection. The modulation of the "typical" appearance of COVID-19 and the decreased severity at imaging in vaccinated individuals with breakthrough infections (6) and certain variants (2) has consequences for clinical expectations of the appearance of COVID-19 pneumonia at imaging. Radiologists must be wary of attributing particular imaging patterns to COVID-19 that may have other etiologies, or excluding consideration of COVID-19 based on unexpected appearances.

"The" disease associated with SARS-CoV-2 infection was dubbed "COVID-19" by the World Health Organization in early 2020. [The authors'] study reminds us that since that time, COVID-19 has

shown variable symptoms, morbidity, and mortality rates, influenced mainly by mutations and changes in host immunity. Spike ("S") protein mutations are most relevant, as the S protein controls binding to the host ACE-2 receptor and is a primary antibody target, affecting host cell binding, and influencing infectivity and virulence. The latest Omicron variants have more than 50 mutations in components of the S protein (7). The World Health Organization names significant SARS-CoV-2 variants with the Greek alphabet, starting with the original Alpha strain, but scientific names follow a "Pangolin" phylogenetic numbering system describing lineage of a strain: for example, the original Alpha variant was B.1.1.7, supplanted by the Delta variant B.1.617.2, and subsequently replaced by the first Omicron variant B.1.1.529. The Omicron variant itself has mutated more rapidly than previous strains (7), and the original B.1.1.529 has largely been replaced by BA.5, which comprises approximately 80% of the circulating virus in the U.S. as of writing, and the BA.4.6 strain, comprising 10% (8). The WHO decision to designate a particular SARS-CoV-2 strain with a Greek letter occurs when characteristics such as infection rate, susceptibility to existing vaccines, and virulence are shown to be significantly different from previous dominant circulating strains. Different "variants of concern" by definition have significantly different properties. This situation is similar to other pandemic agents that have undergone significant mutation. The H1N1 influenza strain that led to the 1918 "Spanish Flu" Pandemic mutated to an endemic "annual flu" strain against which vaccines were developed. In 1947, mutations led to complete vaccine failure and a robust flu season in the United States; subsequent mutations caused several outbreaks, including a 1976 outbreak at Fort Dix (H1N1/New Jersey/76), a 1977 strain that emerged in East Asia, and the notable 2009 variant ((H1N1)pdm09) arising from a triple-reassortment identified in swine in 1998, responsible for the 2009 "swine flu" pandemic (9). Like SARS-CoV-2 variants, these strains had significantly different properties and consequences.

[The author's] study therefore has an implicit cautionary message for interpretation of prior COVID-19 research. Dramatic changes in the landscape of COVID-19 have resulted from a combination

of significant mutations, variable immunity acquired from both infection and vaccination, and improved supportive, antiviral, and other types of therapies. Accordingly, historical bracketing and qualification is now required for previous COVID-19 research. If the severity, appearances, and outcomes of an infection change significantly, is previous work on that infection still relevant? Studies of COVID-19 performed during the first phases of the pandemic describe the characteristics of a novel virus interacting with naive immune systems in the absence of effective therapeutics and vaccines. Which observations are now still accurate, and which will remain relevant in the face of ongoing mutations in SARS-CoV-2 and differences in host response? Which proclamations about the "intrinsic" characteristics of COVID-19 must now be footnoted as pertaining to particular combinations of variants and the immunological landscape of a particular time and region? Are the previously described "typical" characteristics of COVID-19 pneumonia and the manifestations of COVID-19 elsewhere in the body still generalizable? Do previous characterizations of COVID-19-associated vascular disease, including thrombotic phenomena, still apply? Importantly, will "post-acute sequelae of COVID-19" (PASC), including chronic lung disease, be different for those afflicted by different variants and with different vaccination statuses? Additional studies of dominant SARS-CoV-2 variants in increasingly vaccinated and previously infected populations are required for the answers.

Importantly, [the authors'] work also suggests guidelines for future COVID-19 research. At a minimum, research must consider the dominant SARS-CoV-2 strains circulating in the study population, or laboratory identification of viral strains if possible. Data on vaccination status, including a record of primary series and any boosters, and the timing since the last vaccination, given waning of immunity, should be collected and used to inform results. As in [the authors' study], hospitalization *for* COVID-19 is becoming less frequent and hospitalizalization *with* SARS-CoV-2 infection incidental to the main cause of admission is becoming more frequent. Researchers cannot assume that COVID-19 is the primary clinical driver in a patient positive for SARS-CoV-2, and must take care to exclude other possibilities

through careful selection. Of course, this improving trajectory of disease is also subject to change with the rise of new viral variants that may cause more severe disease.

The time for grand proclamations about "the" nature of COVID-19 may be over. However, an era of even more enlightening work on interactions between an ever-changing virus and host immune system may have just begun. The study by [The authors] highlights the way forward.

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