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Clinical Imaging 78 (2021) 142–145

Contents lists available at ScienceDirect

Clinical Imaging

journal homepage: www.elsevier.com/locate/clinimag

Editorial

SARS-CoV-2 reinfection: "New baseline" imaging concept in the era of COVID-19

ARTICLE INFO

Keywords
COVID-19 reinfection
SARS-CoV-2
X-ray
Computed Tomography
Chest
Pneumonia
Residual pulmonary changes
New-baseline imaging

ABSTRACT

Recent reports have suggested COVID-19 relapse or reinfection may lead to readmission, which may cause a diagnostic challenge between recently infected patients and reinfections. Compounding this problem is the post-viral lung sequela that may be expected after COVID-19 pneumonia, similar to both SARS and MERS. Although chest imaging may play a role in the diagnosis of primary SARS-CoV-2 infection, reinfection or relapse of COVID-19 will have similar imaging findings. A "new-baseline" imaging can be obtained from COVID-19 patients at the time of hospital discharge or clinical recovery. This new reference can not only determine if readmissions are from relapse or reinfection of COVID-19, resolving COVID-19 or potentially a different viral infection (influenza), but also for long term sequela of COVID-19 lung infection. Strategic use of imaging before discharge may be helpful in the subset of the population at the highest risk of a secondary viral infection such as influenza. Determining the residual abnormalities in post-discharge imaging can guide us in the long-term management of patients for many years to come.

1. Introduction

The outbreak of novel coronavirus 2019 (SARS-CoV-2), with its epicenter in China, has emerged as a global public health emergency. After Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome (MERS), the novel coronavirus outbreak is the third coronavirus epidemic to have emerged in the past two decades.[1] It was first reported as a cluster of cases with pneumonia of unknown etiology in Wuhan (China) in late December 2019, quickly spreading across other regions of China and worldwide. As of February 1st, the total number of persons infected by the virus has surpassed 103 million, with more than 2.2 million deaths worldwide.[2]

The SARS-CoV-2 virus is a novel coronavirus,[3] but it is suggested to follow the same characteristics of Influenza pandemic progression model.[4] The peak of disease happens at the end of the acceleration phase, followed by a deceleration phase with a decrease in illness. Different countries are in different phases of the pandemic.

Based on current evidence, readmission occurs in COVID-19.[5–21] With a large number of COVID-19 patients recovering from the disease, several cases of suspicious recurrence/relapse have been reported worldwide. These patients present with fever and positive nucleic acid test after a recent hospital discharge, which can lead to diagnostic challenges. In early Chinese studies, the recurrence of SARS-CoV-2 positivity was reported in COVID-19 patients after they met the discharge criteria. As an example, a study by China claimed that 14% of recovered patients had tested positive on the nucleic acid test on re-examination, and factors such as advanced age, poor immune function, and comorbidities were suggested as the major contributors.[18] Similarly, Wang et al. reported 2.29% readmission because of fever or positive SARS-CoV-2 retest.[5] In a case report by Liu et al.,[9] they reported a 108-day follow-up on dynamic clinical manifestation in a COVID-19 patient, who was hospitalized three times due to the positive recurrence of SARS-CoV-2 after discharge.

There continues to be relatively little data to the causes of the re-appearance of SARS-CoV-2 in nasopharyngeal swabs after negative RT-PCR in patients recovered from COVID-19. In earlier studies, it was suggested by some authors that recurrent positive PCR-testing is likely related to insufficient discharge criteria or secondary to sampling errors. They also stated that there was a possibility that the virus had not fully been removed from respiratory tracts at the first discharge, and persistent viral shedding may cause recurrent RNA positivity.[13] As an example, Chen[20] has reported a 46-old-year female developing new-onset fever and respiratory symptoms. Regarding her history of recent travel to Wuhan, a chest CT-scan and an oropharyngeal swab test of SARS-CoV-2 were performed, both of which confirmed COVID-19 infection. After appropriate treatment and symptomatic relief, she underwent two repeated swab tests, which were both negative. Three days later, another PCR-test resulted as positive, while her respiratory symptoms had already improved. She remained under observation in the hospital, and a few days later, her tests were again reported as negative,

Abbreviations: COVID-19, Coronavirus Disease 2019; SARS-CoV-2, Severe Acute Respiratory Syndrome Coronavirus 2; RT-PCR, Reverse Transcription Polymerase Chain Reaction; SARS, Severe Acute Respiratory Syndrome; MERS, Middle East Respiratory Syndrome; CT, Computed Tomography; GGO, Ground Glass Opacification/Opacity.

https://doi.org/10.1016/j.clinimag.2021.03.021
Received 2 October 2020; Received in revised form 2 March 2021; Accepted 18 March 2021
Available online 26 March 2021

and she was discharged. This case might reflect the possibility of false negatives on occasion for pharyngeal swabs tests, affected by various factors such as the sample site, contaminated test samples, and technical errors while taking the swabs. Reinfection, in this case, is an unlikely possibility, regarding the lack of symptoms and the short interval between results. Similar studies support the possibility of false-negative RT-PCR testing results in early case reports.[21]

The most recent studies have demonstrated a few true cases of reinfection. In a case report described by To et al.,[17] clinical, epidemiological, serological (IgG seroconversion), and genomic analyses confirmed reinfection by a different strain of SARS-CoV-2, instead of persistent viral shedding from the first infection (as it was previously thought). Similarly, Tomassini et al.[12] reported two confirmed cases of SARS-CoV-2 reinfection, with 87- and 84-day intervals between their two COVID-19 episodes. Importantly, these cases had two positive SARS-CoV-2 IgG antibody tests, indicating that antibodies were present after the first and persisted through to the second COVID-19 episode, and were, therefore, less likely to be a false positive result.[12]

Further studies have also demonstrated that protective immunity does not happen in all patients infected with SARS-CoV-2, unlike the non-human models,[15,22] leading to the possibility of reinfection with SARS-CoV-2 in recovered patients. Interestingly, in a meta-analysis by Mattiuzzi et al.[10] on 17 studies with 5182 COVID-19 patients, the cumulative rate of SARS-CoV-2 recurrent RNA positivity was estimated to be 12%. They found that nearly one in ten COVID-19 patients might be found positive again within 60 days of recovery from their first infection. They also observed no substantial differences when their analysis was limited to non-Chinese studies. The authors finally concluded that the high reinfection rate signifies the importance of repeated testing for early detection, isolation, and clinical management of cases with recurrent SARS-CoV-2 RNA positivity.

Viral mutations and their role in reinfection are of paramount importance, especially because SARS-CoV-2 vaccines have been developed. The cause of reinfection may be due to multiple factors, which may include virus mutation, but this is not fully been understood, due to the lack of long-term studies.[18] Nevertheless, these case reports prove the significance of re-evaluating and individualizing the current discharge guideline for a subset of patients (based on their clinical and radiographic manifestations). Therefore, the importance of regular clinical assessment of infectivity with or without repeat PCR and radiologic imaging cannot be overemphasized in patients after being discharged, particularly in those who hold a higher risk for severe events after COVID-19 reinfection (old age, comorbidities, undernutrition, lymphopenia, and weak immune reaction with a low or even negative serology).[23,24]

Furthermore, residual clinical and pathological abnormalities after COVID-19 recovery have been reported worldwide, similar to the SARS and MERS findings.[25] A post-mortem case report by Yao et al.[25] found residual pathological features in the lungs of a recovering COVID-19 patient, despite three consecutive negative swab tests. Again, this case emphasizes the importance of dynamic follow-up with clinical, PCR, or radiologic tools in recovering/recovered COVID-19 patients.

2. The role of imaging studies

Pulmonary imaging findings will lag behind clinical improvement. In other words, a patient with COVID-19 with the improvement of symptoms with a subsequent negative test for SARS-CoV-2 may have pulmonary imaging findings that persist for an unspecified time. This may lead to diagnostic challenges for imaging patients with readmission to the hospital. An understanding of the evolution of radiological patterns of the disease from initial infection to recovery is essential.

Based on the earlier publications for COVID-19 diagnosis, chest CT-scan and laboratory PCR testing could be utilized interchangeably, depending on the countries' health care resources and local guidelines.[26] Since the limited availability and quality of laboratory PCR testing in many infected regions remains a challenge, CT-scan had demonstrated by a number of studies to have a high potential to detect the infection.[26,27] However, the current recommendations from organizations such as American College of Radiology (ACR) are against the routine use of CT-scan to diagnose COVID-19.[28] As illustrated in a recent multinational consensus statement from the Fleischner Society, chest CT-scan is now reserved for selective cases in which its findings might change the treatment plan.[29,30] Chest X-rays (CXRs), on the other hand, are the most available imaging modality with acceptable diagnostic performance. Therefore, while chest CTs are potentially useful tools in the management of COVID-19 patients, CXRs will remain the primary diagnostic tool when encountering patients with acute respiratory illnesses.[30]

Imaging manifestations of COVID-19 have been widely debated in numerous publications.[26,27,30] As described in earlier studies, COVID-19 pneumonia frequently presents as multifocal subpleural/peripheral, ground-glass opacities on chest CT-scan. Over time, as the disease continues to progress, the pulmonary opacities can evolve rapidly to bilateral diffuse pulmonary consolidations, with a transition from a pure ground-glass pattern to consolidation or mixed-pattern. Subsequently, increasing the frequency of consolidation patterns will cause it to become the predominant CT-feature. A few patients will then develop a deterioration in the respiratory function, causing ARDS and even death, while in most patients, a radiological reversal process will be started, with regression of consolidations into mixed and finally GGOs (melted sugar sign). Although most patients might eventually have no residual abnormality, some cases will demonstrate pulmonary sequela in the future. It is still unclear when and why the pulmonary healing process disruption might happen in different patients. Similarly, the temporal changes of CXR are strongly correlated with the disease progression, as described by Al-Smadi et al.[30] They reported the common patterns in the evolution of CXR findings with disease progression from peripheral involvement to diffuse, lower to upper zones, and GGOs to consolidations.[30]

Some patients (especially those with underlying comorbidities or older population) who appear to be fully recovered after COVID-19 may continue to have interstitial pulmonary sequela, suggesting the development of fibrosis. Although it is too early to predict the long-term effects of these pulmonary changes, residual pulmonary fibrosis may be present in a subset of COVID-19 patients, similar to the findings in previous studies on the other viral respiratory infections, such as MERS and SARS.[32]

In an observational cohort study by Wu et al.,[31] eleven patients with SARS were followed for up to seven years. The number of pulmonary lesions diminished on follow-up CT-scans performed at 3, 6, and 84 months. They also found that the main CT radiologic findings changed from GGO to fine reticulation predominance, reflecting the interstitial fibrotic proliferation recovery phase after SARS infection. In another study by Tang et al.,[33] five survivors of avian influenza A (H7N9) virus infection underwent chest CT-scan at the discharge time and also six months later. In the follow-up imaging, most of the previous pulmonary abnormalities had been improved; however, multifocal bilateral lesions were still present on all HRCTs. GGOs were the main abnormality, while interlobular septal thickening, subpleural linear opacities, and cystic changes were the second most common findings.

In a long-term follow-up study by Zhang et al.,[34] 71 SARS patients underwent follow-up CT-scan regularly for up to 15 years. They demonstrated that the pulmonary lesions on CT-scans reduced from 2003 to 2004 and remained stable thereafter until 2018. Also, the pulmonary function was correlated with chest CT-scan findings. The patients with residual interstitial pulmonary lesions had lower pulmonary function tests compared to those without sequels. Similar post-viral pulmonary residues, including GGOs, interseptal thickenings, and fibrotic bands, have been shown in other studies.[35,36] Thus, we might expect COVID-19 to act in a similar fashion.

As mentioned above, pulmonary imaging abnormalities are highly

likely to persistent in recovered COVID-19 patients. Early studies indicate that post-discharge/recovery radiologic imaging still reveals some abnormalities in recovered patients.[32,37] In a study with 348 COVID-19 patients, 98.01% had lung abnormalities on chest CT after 28 days.[37] The likelihood of residual pulmonary lesions after COVID-19 recovery will create additional challenges for imaging diagnosis between resolving pulmonary infection, reinfection with COVID-19 or a different virus (influenza). The use of a "new-baseline" imaging (preferably using CXR due to lower radiation) for high-risk patients can offer a snapshot of pulmonary findings either at the time of discharge or a follow-up examination. This could be especially important during the flu season, since influenza could cause similar clinical and radiological abnormalities as COVID-19. The Fig. 1 reveals a non-resolved pulmonary lesion 67 days after COVID-19 recovery. In the absence of a baseline imaging (Fig. 2), this lesion could be interpreted as either a new primary viral infection or residual lung damage from the previous COVID-19. Indeed, chest imaging at the time of discharge (Fig. 2) would act as a new-baseline study for future comparison. The utility of reimaging would help distinguish a second infection from non-resolved opacity, if different parts of the lung are infected or if ground-glass opacities transition back to consolidation.

Strategic use of imaging before discharge may be helpful in the subset of the population at the highest risk of secondary viral infection or lung residual deficits and/or have comorbidities (including older patients, having comorbidities such as hypertension and diabetes, patients with a lower immune system, or lower levels of antibodies in the first episode).[38–41]

Finally, it should be noted that the present manuscript suffers from some inherent biases, such as the incidental reported cases of reinfection, limitations of reviewed retrospective studies, the lack of multi-institutional studies to determine the true rate of reinfection (probably supported by viral serological markers for possibility of infection with a new serology). Long-term prospective studies are needed so, in order to evaluate the value of new-baseline imaging, as described in the paper.

3. Conclusion

While the natural history of COVID-19 has not yet been fully explored, and long-term radiological follow-up studies are needed to confirm these findings, the potential added value of a new-baseline chest radiography in patients who are recovered from SARS-CoV-2 infection cannot be overemphasized. The method of utilizing this new reference will assist the clinicians in facing possible future challenges. This may predict long-term pulmonary function, but also new-baseline chest imaging can guide us in a better decision when encountering lung abnormalities on follow-up imaging of patients who once had COVID-19. Therefore, we suggest chest imaging at the time of discharge or shortly thereafter in patients at the highest risk of secondary viral infection and/or have comorbidities. This baseline imaging might also be of great value for continued surveillance of post-discharge COVID-19 patients. Determining the residual abnormalities in post-recovery imaging (specifically using CXRs as the main imaging tools due to its lower radiation, unless CT scans had been performed for other reasons) will guide us in the long-term management of these patients for many years to come.

Funding

None.

Ethics approval

Not applicable.

Consent to participate and/or publication

Not applicable.

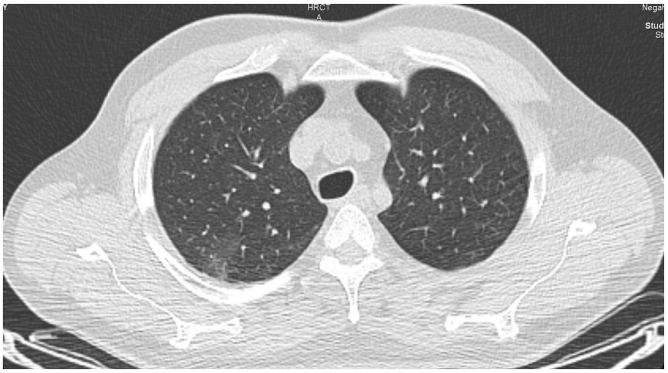

Fig. 1. A 68-year-old man, presented 67 days after being discharged for COVID-19. Axial chest CT imaging reveals a mild ground glass opacity involving the right upper lobe.

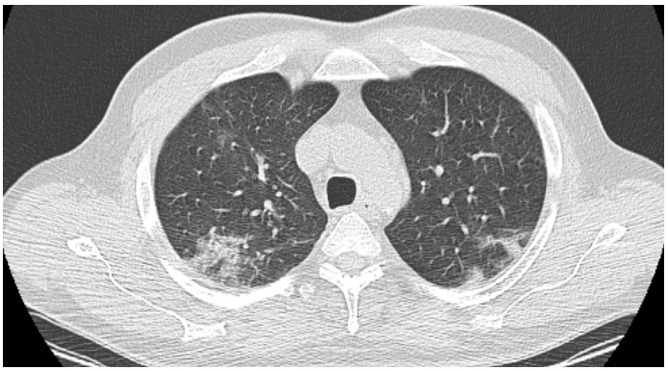

Fig. 2. The initial CT images of patient 1 reveals bilateral multifocal consolidations, in favor of COVID-19 infection.

Declaration of competing interest

The authors have no conflicts of interest relevant to this article to disclose.

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