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**Augmentation of literature review of COVID-19 radiology**

Merchant SA *et al*. Augmentation of COVID-19 imaging literature

**Abstract**

We suggest an augmentation of the excellent comprehensive review article titled "Comprehensive literature review on the radiographic findings, imaging modalities, and the role of radiology in the COVID-19 pandemic" under the following categories: (1) "Inclusion of additional radiological features, related to pulmonary infarcts and to COVID-19 pneumonia"; (2) "Amplified discussion of cardiovascular COVID-19 manifestations and the role of cardiac MRI in monitoring and prognosis"; (3) "Imaging findings related to Fluorodeoxyglucose Positron Emission Tomography, Optical, Thermal and other Imaging modalities/devices, including 'Intelligent Edge' and other remote monitoring devices (RMDs)"; (4) "Artificial Intelligence (AI) in COVID-19 imaging"; (5) "Additional Annotations to the Radiological Images in the manuscript to illustrate the additional signs discussed"; and (6) "A minor correction to a passage on pulmonary destruction".

Merchant SA, Nadkarni P, Shaikh MJS. Augmentation of literature review of COVID-19 radiology. *World J Radiol* 2022; In press

**Core Tip:** Utility of classical radiographic findings suggestive of coronavirus disease 2019 (COVID-19) mediated pulmonary infarction - Hampton's hump, Westermark sign; and Subpleural sparing, Reversed halo sign - should improve the diagnostic accuracy of identification of COVID-19 pulmonary complications. This gain in accuracy would apply whether these findings are seen on plain Chest X-Ray or computed tomography: The former is important in financially constrained locales with limited medical-technology infrastructure. Distinctive COVID-19-associated coagulopathy is more frequent with

worsening disease severity in COVID-19. Cardiac magnetic resonance imaging can play an important role in monitoring and prognosis. "Artificial Intelligence (AI) in COVID-19", "'Intelligent Edge' and other remote monitoring devices (RMDs)" are also discussed.

## TO THE EDITOR

We compliment Pal *et al*[1] for their excellent review. It is a comprehensive review indeed. An excellent effort with great details, including in depth pathophysiology, detailed illustrations *etc.* Their coverage of imaging modalities is quite extensive too and includes a detailed look into the role of ultrasound in coronavirus disease 2019 (COVID-19), including point of care ultrasound, an invaluable addition. For the benefit of your readers, we wish to augment their excellent work and submit the following suggestions for the benefit of your readers.

## INCLUSION OF ADDITIONAL RADIOLOGIC FEATURES

We are involved in an ongoing multicentric international study on COVID-19 chest imaging and developing artificial intelligence (AI) algorithms for diagnosis, risk stratification, monitoring, prognostication *etc.* Our 2020 publication has described additional important and distinctive COVID-19 chest-imaging features[2]. These include the following, seen on both plain chest radiographs and computed tomography (CT).

*Classic signs of pulmonary infarcts*

**Hampton's hump:** Triangular/wedge shaped opacities with their bases towards the periphery of the lung/Lobe/Lobule. This sign has sensitivity and specificity of 22% and 82% respectively[3,4].

**Westermark sign:** Oligemia - a rarefied area due to blood vessel collapse - distal to the site of occlusion by a pulmonary embolus. This sign has sensitivity and specificity of 14% and 92%[3,5].

**Palla's sign:** An enlarged right pulmonary artery, suggesting embolism of segmental/subsegmental pulmonary arteries when seen together with Westermark's sign: Sensitivity is reported to be "low" and specificity unknown. These findings are likely due to the microvascular thrombosis propensity in COVID-19[6-8], as discussed below, leading to a relatively increased incidence of pulmonary thromboembolism in COVID-19 pneumonia patients[9].

It is time to revisit these time-tested radiological signs for pulmonary infarcts[2]. Utilizing classic signs of infarcts and pneumonia will increase diagnostic accuracy and also help raise awareness about the utility of chest radiographs', even in the current era; especially in cost-constrained locales lacking sophisticated infrastructure. It will also help develop more accurate AI algorithms for diagnosis/prognosis of COVID-19. Co-occurrences of these signs are uncommon across COVID-19 patients: When seen in tandem, however, they may constitute a highly specific diagnostic signature. This speculation, of course, needs validation by larger studies.

## SIGNS ASSOCIATED WITH COVID-19 PNEUMONIA

### Subpleural sparing

Reported in 23% of COVID-19 cases in an Iranian study[10], is commonly associated with Non-specific interstitial pneumonia, and described with lung contusions, pulmonary alveolar proteinosis, severe acute respiratory syndrome (SARS), and pneumocystis jirovecii infection[11]. The specificity of this finding depends on the prior probability of COVID based on molecular detection *via* polymerase chain reaction (PCR).

### Reversed halo sign

A focal ring-shaped area of ground-glass opacity within a peripheral rim of consolidation, suggesting an organizing/healing pneumonia[12]. It offers prognostic potential in COVID-19[13,14]. Data on sensitivity/specificity are not currently available. Utilizing classic signs of infarcts and pneumonia will increase diagnostic accuracy, and also help raise awareness about chest radiographs' utility, even in the current era,

especially in cost-constrained locales lacking sophisticated infrastructure. It will also help develop more accurate AI algorithms for diagnosis/prognosis of COVID-19. Co-occurrences of these signs are uncommon across COVID-19 patients: When seen in tandem, however, they may constitute a highly specific diagnostic signature. This speculation, of course, needs validation by larger studies.

## ADDITIONAL ANNOTATION TO IMAGES

The paper's images show the following (currently unannotated) features. Subpleural sparing: Figure 4B [just under arrow marked as ground glass opacities (GGO)], 7C and 7F. Hampton's humps: Figures 2E, 2F, 4B (marked as consolidation), 4C, and 7A (larger, but fewer, in the right lung than left lung). Westermark sign: Figure 2F. Pericardial air: Figure 2C.

## AMPLIFIED DISCUSSION OF CARDIOVASCULAR AFFECTION BY COVID

*Distribution of cardiovascular angiotensin-converting enzyme 2 receptors and pathophysiology impact*

While correctly noting the ability of the coronavirus SARS-CoV-2, the causative agent of COVID-19, to invade cells by binding with high affinity to angiotensin-converting enzyme 2 (ACE2) and transmembrane protease serine 2 receptors, the authors have not discussed the cardiovascular system, where COVID-19's impact has been reviewed widely[6,15-17]. The ACE2 receptor is also expressed in the cardiovascular system: The endothelium of coronary arteries, cardiomyocytes, cardiac fibroblasts, epicardial adipocytes, vascular endothelial, and smooth muscle cells[18-20].

Binding of SARS-CoV-2 to endothelium predisposes to micro-thrombosis *via* endothelial inflammation, complement activation, thrombin generation, platelet, and leukocyte recruitment, and initiation of innate and adaptive immune responses lead to micro-thrombosis with complications such as: Deep vein thrombosis, pulmonary embolism, cortical venous thrombosis, stroke, cardiac inflammation and injury, arrhythmias, and blood clots[18], and acute/chronic myocardial injury[21]. Assay of the

fibrin degradation product D-dimer (a thrombosis marker) on admission for prognostication of in-hospital mortality is now mandated in most clinical protocols to differentiate mild from severe COVID-19[7,22], especially when coupled with thrombocytopenia[8]. In infants and children reports of coronary artery aneurysms (CAA), including giant CCAs are gathering momentum as a part of Multisystem Inflammatory Syndrome in post COVID 19 children (MIS-C)[23-26].

## ROLE OF CARDIAC & THORACIC MAGNETIC RESONANCE IMAGING

While the authors correctly note that cardiac magnetic resonance imaging (MRI) may be useful in future to detect complications in patients with abnormal echocardiography, this is a current need too. Up to 60% of hospitalized COVID-19 patients have been reported to have evidence of myocardial injury[21] (Figure 1A). Among post-discharge patients, approximately 10% complain of palpitations, with half of these having ongoing chest pain 6 mo after discharge[15]. Dilated cardiomyopathy is a known complication of COVID cardiac injury[27] (Figures 1B and 1C). In post-COVID-vaccination patients, distinct self-limited myocarditis and pericarditis have appeared. While myocarditis developed rapidly in younger patients, mostly after the second vaccination, pericarditis affected older patients later, after either the first or second dose[28]. A recent report implicates the booster dose of the COVID-19 vaccine for acute myocarditis too[29]. In infants and children with COVID-19 reports of CAAs, including giant CAAs are gathering momentum[23-26]; and cardiac MRI/CT can be an invaluable in diagnosing these too. This is particularly important as these aneurysms (and their catastrophic consequences) are potentially regressible with 'steroid therapy'. In addition these aneurysms would need to be monitored and managed; including for their potential to develop thrombosis[24]. Management includes cardiac support, immunomodulatory agents, and anticoagulation[26]. Richardson et al[24] stated that in infants, rapidly progressing CAAs are noted post COVID-19 infection. They also stated that as opposed to published reports, these may be seen even in the absence of haemodynamic instability, ventricular dysfunction, myocardial ischaemia or myopericarditis. In view of the risk of progression

of cardiac signs and symptoms, Sperotto *et al*[26] recommended long-term follow-up of these patients. Coronary arteries should therefore be thoroughly assessed in patients presenting with MIS-C symptoms[25]. For its non-ionizing radiation nature MRI would be the first choice in children. However, CT on account of its speed (and current low radiation protocols) can be utilized effectively too (Figure 1D).

In their Radiology 2021 editorial, Lima *et al*[30] state that prolonged symptoms due to "long-haul" COVID-19 portend the potential for chronic cardiac sequelae, whose duration and severity remain unknown. They introduce the work of Kravchenko *et al*[31], which demonstrates cardiac MRI's value in identifying inflammation, adverse patterns of hypertrophy, fibrosis, and myocardial injury due to myocarditis, pericarditis, and cardiomyopathy, and healing.

Although thoracic CT is widely used for imaging of COVID-19 infection, thoracic MRI can also be used as an alternative diagnostic tool because of its advantages[32]. This is particularly important in patients requiring avoidance of exposure to ionizing radiation; *e.g.*, in children and during pregnancy where pulmonary MRI may be preferred over pulmonary CT[33]. Pulmonary abnormalities caused by COVID-19 pneumonia can be detected on True FISP MRI sequences and correspond to the patterns known from CT. Spiro *et al*[34] have made a useful suggestion for the current pandemic: Following MRI of the abdomen or heart, there should be careful evaluation of the visualised parts of the lungs for COVID-19 findings. This would enable the identification and isolation of undetected cases of COVID-19. Necker *et al*[35] have reported cinematic rendering of SARS-CoV-2 pneumonia. Cinematic rendering is a digital 3D visualization technique that converts grayscale slices from CT or MRI into colored 3D volumes *via* transfer functions illuminating the reconstruction with physical light simulation. They have stated that this type of rendering produces a natural, photorealistic image that is intuitively understandable and can be well applied for clinical purposes. Cinematic rendering of CT images is a new way to show the three dimensionality of the various densities contained in volumetric CT/MRI data; and we agree with them and feel that such cinematic

rendering can make complicated volume rendered CT/MRI images easy to understand for other clinicians, administrators, policy makers, as well as patients alike.

## ROLE OF 18-FLUORODEOXYGLUCOSE POSITRON EMISSION TOMOGRAPHY

The authors' suggestion of using fluorodeoxyglucose-positron emission tomography (FDG-PET) in future for prognosis and monitoring is wonderful. We wish to add that the "Rim Sign" - a slight and continuous FDG uptake at the border of a peripheral lung consolidation[36] - is easily recognisable at FDG-PET/CT (though data on sensitivity/specificity are not available). When present, it strongly suggests pulmonary infarction and is observable even without suggestive finding of pulmonary infarction. The Reverse Halo sign would also be seen. Though highly sensitive, use of PET/CT for primary detection of COVID-19 is constrained by poor specificity, as well as considerations of cost, radiation burden, and prolonged exposure times for imaging staff. However, in patients who may require nuclear medicine studies for other clinical indications, PET imaging may yield the earliest detection of nascent infection in otherwise asymptomatic individuals. This may be extremely vital for immunocompromised patients, including those with co-existent malignancies, where the early diagnosis of infection and subsequent initiation of care needed will contribute vitally to improving outcomes and reducing morbidity and mortality[33].

### Role optical, thermal imaging and other remote patient monitoring devices

Lukose et al[37] stated that the currently popular method of collecting samples using the nasopharyngeal swab and subsequent detection RNA using the real-time PCR has false-positive results and a longer diagnostic time frame; and that various optical techniques such as optical sensing, spectroscopy, and imaging show great promise in virus detection; and that the progress in the field of optical techniques for virus detection unambiguously show a great promise in the development of rapid photonics-based devices for COVID-19 detection. They also provided a comprehensive review of the various photonics technologies employed for virus detection, especially the SARS-CoV family; such as:

Near-infrared spectroscopy, fourier transform infrared spectroscopy, raman spectroscopy, fluorescence-based techniques, super-resolution microscopy, surface plasmon resonance-based detection.

Gomez-Gonzalez et al[38] have reported a proof of concept of optical imaging spectroscopy for rapid, primary screening of SARS-CoV-2. A study by Shah et al[39] found that home pulse oximetry monitoring identified the need for hospitalization in initially non-severe COVID-19 patients when a cut-off of $SpO_2$ 92% was used and that home $SpO_2$ monitoring also reduced unnecessary Emergency Department revisits. McKay et al[40] stated that due to its portability, affordability, and potential to serve as a screening tool for a conventionally lab-based invasive test, the mobile phone capillaroscope could serve as an important point-of-care tool and that the simplicity and portability of their technique may enable the development of an effective non-invasive tool for white blood cell (WBC) screening in point-of-care and global health settings. This would be extremely useful in the COVID-19 pandemic scenario as WBC monitoring forms an essential part of COVID-19 management and follow-up[41,42].

Infrared thermography has been considered a gold standard method for screening febrile individuals during the pandemics since the SARS outbreak in 2003. Khaksari et al[43] showed that in addition to an elevated body temperature, a patient with COVID-19 will exhibit changes in other parameters such as oxygenation of tissues; and cardiovascular and respiratory system functions. They also promulgated a compelling need to develop a new technique that would have the ability to screen all these signals and utilize the same for early detection of viral infections. In their opinion, keeping the advent of wireless technologies in mind, the development of such sensors that have point-of-care home-accessible capabilities will go a long way in better managing the increasing numbers of patients with COVID-19 who are opting for home quarantine and that this will eventually reduce the burden on the healthcare system.

The COVID-19 pandemic is changing the landscape of healthcare delivery worldwide. There is a discernible shift toward remote patient monitoring (RPM). It is pertinent to note that a large number of RPM platforms are already utilising optical technologies[44].

This area of research has great potential for growth and the biomedical optics community has great prospects in the development, testing, and commodification of new wearable RPM technologies; to add to the available healthcare armamentarium and contribute to the rapidly changing healthcare and research environment, not just for the COVID-19 era, but far beyond[44].

Various other ingenious methods/modalities have been used for early detection/screening for COVID-19. These include smartwatches[45], smart phones and other Intelligent Edge devices. Mishra *et al*[45] developed a method utilising data from smartwatches to detect onset of COVID-19 infection in real-time that detected 67% of infection cases at or before symptom onset. They stated that their study provided a roadmap to a rapid and universal diagnostic method for the large-scale detection of respiratory viral infections in advance of symptoms, highlighting a useful approach for managing epidemics using digital tracking and health monitoring. Seshadri *et al*[46] stated that when used in conjunction with predictive platforms, wearable devices users could receive alerts when changes in their metrics match those related to COVID-19 and that such anonymous data localized to regions such as neighbourhoods or zip codes could provide public health officials and researchers a valuable tool to track and mitigate the spread of the virus. Their manuscript describes clinically relevant physiological metrics that can be measured from commercial devices today and highlights their role in tracking the health, stability, and recovery of COVID-19 + individuals and front-line workers. Schuller *et al*[47] in their paper tilted 'COVID-19 and Computer Audition: An Overview on What Speech & Sound Analysis Could Contribute in the SARS-CoV-2 Corona Crisis' provide an overview on the potential for computer audition (CA), *i.e.*, the usage of speech and sound analysis by AI to help in the COVID-19 pandemic scenario and concluded that CA appears ready for implementation of (pre-)diagnosis and monitoring tools, and more generally provides rich and significant, yet so far untapped potential in the fight against COVID-19 spread.

AI in COVID 19 imaging: Telemedicine has advanced by leaps and bounds. AI algorithms enable faster diagnosis (including remote diagnosis), with a fair degree of

accuracy[48]. While the application of AI to medical imaging of cancers and other diseases is being developed over the past decades, the recent COVID-19 pandemic hastened the: (1) Need; (2) Development; (3) Training; and (4) Testing of AI algorithms, within a relatively shorter time-span of less than two years[49]. This was extremely beneficial for radiologists and other physicians involved in performing rapid diagnosis, keeping in mind this was a time when there was immense overloading of the healthcare system[50]. The benefits including for management, were obvious. However limitations such as: (1) Limited datasets; (2) Inaccurate execution of training and testing procedures; and (3) Use of incorrect performance criteria needed to be dealt with. The above limitations can be overcome by the utilisation of federated learning (FL)[48,51,52].

The technique of FL was originally pioneered by Google[53] as an application of their well-known MapReduce algorithm[54] and allows for iteratively training an ML model across geographically separated hardware, including mobile devices: The ML algorithm is distributed, while data remains local. It can be employed for both statistical and deep learning. Despite its drawbacks - specifically, wide-area network bandwidth limits computation speed - FL appears to be a great way forward, especially for multi-centre collaborations, getting around the 'tricky' data privacy issue, enabling algorithms/outcomes with much more accuracy than otherwise possible[51].

If AI is to make an even greater impact Merchant *et al*[48] suggest getting down to the basics and incorporating time tested key medical 'teaching' and/or key 'clinical' parameters, including prognostic indicators, for more effective AI algorithms and their better clinical utility. They also stated that "Artificial Intelligence needs real Intelligence to guide it"! Combining the wisdom gained over the years, with the immense versatility of AI algorithms will maximize the accuracy and utility of AI applications in medical diagnosis and treatment modalities. We have gained wisdom regarding COVID-19 imaging over the past few years and should utilize the same for creation of better algorithms - for screening/detection/prognostication and management.

El Naqa *et al*[55] as part of a Medical Imaging Data and Resource Center initiative, noted that the pandemic has led to the coupling of inter-disciplinary experts that include: (1)

Clinicians; (2) Medical physicists; (3) Imaging scientists; (4) Computer scientists; and (5) Informatics experts. All of whom are working for solving the challenges of the COVID-19 pandemic, specifically, AI methods applied to medical imaging. They stated that the lessons learned during the transitioning to AI in the medical imaging of COVID-19 can inform and enhance future AI applications, making the entire transitions more than every discipline combined to respond to emergencies like the COVID-19 pandemic. AI has been used in multiple imaging fields for COVID-19 imaging.

Manokaran *et al'* model could achieve an accuracy of 94% in detecting COVID-19 and an overall accuracy of 92.19%, which is based on DenseNet201[56]. The model can achieve an area under receiver operating characteristic curve (AUC) of 0.99 for COVID-19, 0.97 for normal, and 0.97 for pneumonia. Their automated diagnostic model yielded an accuracy of 94% in the initial screening of COVID-19 patients and an overall accuracy of 92.19% using chest X-ray images.

Kusakunniran *et al*[57] proposed a solution to automatically classify COVID-19 cases in chest X-ray images using the ResNet-101 architecture was adopted as the main network with over 44 millions parameters. A heatmap was constructed under the region of interest of the lung segment, to visualize and emphasize signals of COVID-19. Their method achieved a sensitivity, specificity, and accuracy of 97%, 98%, and 98%, respectively. Rao *et al*[58] stated that separable SVRNet and separable SVDNet models greatly reduce the number of parameters, while improving the accuracy and increasing the operating speed.

Yi *et al*[50] utilized a large CT database (1112 patients) provided by China Consortium of Chest CT Image Investigation, and investigated multiple solutions in detecting COVID-19 and distinguishing it from other common pneumonia and normal controls. They compared the performance of different models for complete and segmented CT slices, in particular studying the effects of CT-superimposition depths into volumes, on the performance of their models and showed that an optimal model can identify COVID-19 slices with 99.76% accuracy (99.96% recall, 99.35% precision, and 99.65% F1-score).

Chaddad *et al*[59] investigated the potential of deep transfer learning to predict COVID-19 infection using chest CT and X-ray images. They opined that combining chest CT and

X-ray images, DarkNet architecture achieved the highest accuracy of 99.09% and AUC of 99.89% in classifying COVID-19 from non-COVID-19 and that their results confirmed the ability of deep convolutional neural networks with transfer learning to predict COVID-19 in both chest CT and X-ray images. They concluded that this approach could help radiologists improve the accuracy of their diagnosis and improve overall efficiency of COVID-19 management.

Cho et al[60] performed quantitative CT analysis on chest CT images using supervised machine-learning to measure regional GGO and inspiratory and expiratory image-matching to measure regional air trapping, in survivors of COVID-19. They summarized that quantitative analysis of expiratory chest CT images demonstrated that small airways disease with the presence of air trapping is a long-lasting sequelae of SARS-CoV-2 infection.

Fuhrman et al[61] developed a cascaded transfer learning approach to extract quantitative features from thoracic CT sections using a fine-tuned VGG19 network where a CT-scan-level representation of thoracic characteristics and a support vector machine was trained to distinguish between patients who required steroid administration and those who did not. They demonstrated significant differences between patients who received steroids and those who did not and concluded that their 'cascade deep learning method' has great potential in clinical decision-making and also for monitoring of patient treatment.


**THE FUTURE**

Quantum Computers and Quantum microscopes, new quantum repeaters enabling a scalable super secure Quantum Internet (distance will no longer be a hindrance, not just Internet of things but 'Intelligent Edge' devices commonplace[62]); will give a quantum boost to COVID-19 and other health-care algorithms/strategies, including in other related fields, improving healthcare in ways beyond the realm of dreams[51]. Cloud computing could be complemented by Edge Computing, taking advantage of the burgeoning Intelligent Edge devices (smartphones are common place in the remotest of

locations). [15] Besides latency, edge computing is preferred over cloud computing in remote locations, where there is limited or no connectivity to a centralized location; a requirement of cloud computing , which require local storage, similar to a mini data centre at their locations[63]. Medical imaging including COVID-19/other pandemic imaging & AI will never be the same again, in the era of Quantum Computing and Quantum Artificial Intelligence, Medical Imaging & Healthcare will reach stratospheric levels, and beyond[47].

Correction: "Pulmonary destruction": The author's state: "The migration of fluid into the alveolar sacs is governed by the imbalance in Starling forces. The diffuse alveolar damage caused by the viral particles results in an increased capillary wall permeability (high $k$ value), thereby increasing the force at which fluid migrates from the capillaries to the alveolar space.", emphasis added. Surely the authors mean "rate" instead of "force". Permeability is the inverse of resistance. By analogy with Ohm's Law for electricity (current = voltage/resistance) or its equivalent for blood pressure (cardiac output=blood pressure/peripheral resistance), capillary outflow will increase under fixed/constant pressure if permeability increases. We hope that this augmentation of the excellent review by Pal *et al*[1] will enhance your readers' ability to evaluate COVID-19 patients on imaging. COVID 19 is here to stay with us for long: Each effort at adding to the information available in the literature will go a long way in improving patient care overall.

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