

Dear Editor

We thank the reviewers for the valuable inputs and have incorporated all their suggestions, including minor language polishing. These are as stated below: **Manuscript No.: 74112**

Reviewer #1: Conclusion: major revision

Specific Comments to Authors: Thank you for the opportunity to review your manuscript. Although it is a good summary in general, I think that thoracic MRI should be added to the article as well as cardiac MRI. The following articles can be used in this regard. (1) Ates OF, Taydas O, Dheir H. Thorax Magnetic Resonance Imaging Findings in Patients with Coronavirus Disease (COVID-19). Acad Radiol. 2020 Oct;27(10):1373-1378. (2) Fields, Brandon KK, et al. "Imaging of COVID-19: CT, MRI, and PET." Seminars in Nuclear Medicine. Vol. 51. No. 4. WB Saunders, 2021. (3) Spiro, Judith Eva, et al. "Appearance of COVID-19 pneumonia on 1.5 T TrueFISP MRI." Radiologia Brasileira 54 (2021): 211-218.

We thank reviewer # 1 for appreciating our work. The valuable inputs received have been incorporated. All of the references mentioned above have been gone through and quoted from - [Reference nos.-pl refer above: (1) = 32, (2) = 33 and (3) = 34]

Reviewer #2: Conclusion: Accept (General priority)

Specific Comments to Authors: there are no specific comments

We thank reviewer # 2 for going through our manuscript and recommending acceptance of the same.

Reviewer #3: Conclusion: Rejection

Specific Comments to Authors: I do not think radiological signs is so important in daily clinical practice, the review have already provided enough information for radiologists and clinicians. we cannot provide too much information in one paper.

We thank reviewer # 3 for reviewing our manuscript. We humbly disagree with his opinion: It is well known (and all good radiology teachers will agree with the same) that radiological signs are extremely vital; and familiarity with these signs are a great boon

in arriving at a diagnosis in day to day clinical practice. Besides Journal articles are also read by radiology trainees; and not just qualified radiologists and other clinicians.

Reviewer #4: **Conclusion:** Minor revision

Specific Comments to Authors: The manuscript was conceived to amend an excellent review by Pal et al, recently published in the World Journal of Radiology (A. Pal et al., World J Radiol, 2021, 13(9): 258-282). The authors point to some additional radiological findings when COVID is diagnosed through chest radiography (CXR) and computed tomography (CT), which were not mentioned by the authors of the review. They also note the role the other methods of medical imaging play in COVID detection. These are magnetic resonance imaging (MRI) and positron emission tomography (PET). Such an amendment seems quite relevant and appropriate. The text is concrete and written in good English. In principle, I like everything the authors wrote. But just the economy of words leaves an impression that something remains hidden. In this context the manuscript has more the semblance of a review to the above review paper, as if they found errors in the review and want them to be corrected. But it is not actually so. The review by Pal et al is really good and needs no revision at all. I would recommend the authors of the manuscript to think how they could improve and extend their text in order to wear off such an impression. In my view, this can be done in two directions.

First, extend the range of medical imaging methods by adding, for example, optical imaging and thermography. For this purpose it would be appropriate to refer to the following papers: (i) T. Mishra et al, Preprint medRxiv 2020.07.06.20147512, 2020; (ii) X. Zheng et al, Front Digital Health 2: 8, 2020; (iii) S. Shah et al, Acad Emerg Med 27: 681-692, 2020; (iv) G.N. McKay et al, Biomed Opt Express 11(4): 2268-2276, 2020; (v) D. Roblyer, J Biomed Opt 25(10): 102703, 2020; (vi) K. Khaksari et al, J Med Imaging 8(S1): 010901, 2021. **Second. The review briefly discusses the role of artificial intellect (AI) in COVID detection and classification. However the topic can and, in my view, must be covered wider.** In this respect I can recommend the (0) Special Issue of the Journal of Medical Imaging “Medical Imaging of COVID-19” (2021) and, in particular, the following publications: (1) I.E. Naga et al, J Med Imaging 8(S1): 010902, 2021; (2) W. Kusakunniran et al, J Med Imaging 8(S1): 014001, 2021; (3) J.D. Fuhrman et al, J Med

Imaging 8(S1): 014501, 2021; (4) A. Chaddad et al, J Med Imaging 8(S1): 014502, 2021; (5) Q. Hu et al, J Med Imaging 8(S1): 014503, 2021; (6) Y. Li et al, J Med Imaging 8(S1): 017502, 2021; (7) J. Manokaran et al, J Med Imaging 8(S1): 014503, 2021; (8) K. Rao et al, J Med Imaging 8(S1): 017504, 2021. After improvement the manuscript can be published in the *World Journal of Radiology*.

We thank reviewer # 4 for going through our manuscript and giving us invaluable inputs. We definitely agree that Pal et al's review is "excellent". We have stated this at the outset, along with reasons for the same. However, suggestions by Reviewer # 4 are well stated and we have incorporated the same; including additional references and a minor revision in the title to reflect what he had suggested. In view of his suggestion this manuscript may be published as an addendum/continuation of Pal et al's excellent article. We leave it to the editors to take a decision on the same and publish it as a mini-review (augmenting the earlier detailed review) and amend the title further, if required.

1. **The suggested references for medical imaging methods are incorporated thus:**
(i) = Bibliography Ref # 44, (ii) = 46 (we could not find the above reference but found another excellent one Schuller et al - with Zeng as a co-author), (iii) =38 , (iv) = 39 , (v) = 43, (vi) = 42. In addition a few more references have been added (pl refer to the section of Optical, Thermal Imaging etc)
2. **For suggested references for Artificial Intelligence are incorporated thus:** (0)= Bibliography Ref #48, (1) =54 , (2) = 56 & (3) = 59, (4)=58, (6)= 49, (7)=55, (8)=57. However, we have chosen not to cite Q. Hu et al [refer (5) above] as: (a) their work is too complex for the scope of this manuscript & (b) their purpose also was: 'We propose a deep learning method for the automatic diagnosis of COVID-19 at patient presentation on chest radiography (CXR) images and **investigate the role of standard and soft tissue CXR in this task**'; and they concluded that: "**inclusion of soft tissue images did not result in a significant performance improvement**". However we have quoted from the excellent editorial by Maryellen Giger, very elegantly written for this special issue (ref 48).

3. A minor revision in the title reflects the suggestion that this manuscript may be published as an addendum/continuation of Pal et al's excellent article. We leave it to the editors to decide on the same and publish it as a mini-review (augmenting the earlier detailed review) and amend the title further, if required.

Re-reviewer: **Conclusion:** Accept

Specific Comments to Authors: Suggested changes have been made in the article, and as such, I do not have any additional suggestions.

Thanks for your comments.

Science editor:

It is suggested that thoracic MRI should be added to the article as well as cardiac MRI; expand the scope of medical imaging methods; enrich the discussion of the role of artificial intelligence (AI) in COVID detection and classification.

We have incorporated all the changes suggested by the Science Editor (added Thoracic MRI, expanded the scope of Medical Imaging methods and further enriched the role of artificial intelligence (AI).

Company editor-in-chief:

I have reviewed the Peer-Review Report, full text of the manuscript, and the relevant ethics documents, all of which have met the basic publishing requirements of the World Journal of Radiology, and the manuscript is conditionally accepted. I have sent the manuscript to the author(s) for its revision according to the Peer-Review Report, Editorial Office's comments and the Criteria for Manuscript Revision by Authors.

We have revised the manuscript according to the peer review report, the Editorial Offices comments (as detailed above), and the criteria for manuscript revision have been followed.

We appreciate the efforts of all reviewers and thank them for their contribution in raising the level of our manuscript. We have 3 figures and additional text as described above; including a brief note on the 'rising incidence' of Coronary artery aneurysms in

infants and children – post COVID 19, as a part of Multisystem Inflammatory Syndrome in Children – to the cardiac section. We have highlighted smaller changes made in the manuscript to enable easier reviewing. For the larger changes we have highlighted the title of that particular section./segment.

Title: Augmentation of Literature Review of COVID-19 Radiology :

Pal et al¹, World J Radiol 2021

Manuscript No.: 74112

Running Title: Augmentation of COVID-19 Imaging Literature

Abstract:

We suggest an augmentation of the excellent comprehensive review article of Pal et al¹ under the following categories:

- Inclusion of Additional Radiological Features, related to pulmonary infarcts and to COVID-19 pneumonia.
- Amplified discussion of cardiovascular COVID-19 manifestations and the role of cardiac MRI in monitoring and prognosis.
- Imaging findings related to Fluorodeoxyglucose Positron Emission Tomography, Optical, Thermal and other Imaging modalities/ devices , including 'Intelligent Edge' and other remote monitoring devices (RMDs).
- Artificial Intelligence (AI) in COVID-19 imaging
- Additional Annotations to the Radiological Images in the manuscript to illustrate the additional signs discussed.
- A minor correction to a passage on pulmonary destruction.

Keywords

COVID-19 Radiological Findings; Chest Radiographs; Hamptons Hump; Westermark Sign; Computed Tomography; Cardiac Magnetic Resonance Imaging; COVID-19-associated coagulopathy; COVID-19 Imaging; AI in COVID-19.

Core Tips:

- The use of classical radiographic findings suggestive of COVID-19 mediated pulmonary infarction – Hampton’s Hump, Westermark Sign, Palla’s 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 CT: 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. Thrombotic events frequently occur in COVID-19 and are associated with increased disease severity and worsened clinical outcomes. Given that 60% of COVID-19 admissions have cardiac manifestations, Cardiac MRI can play an important role in monitoring and prognosis. The role of other imaging methods, including ‘Intelligent Edge’ and other remote monitoring devices (RMDs); and Artificial Intelligence (AI) in COVID-19 are also discussed.

We compliment Pal A 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 COVID 19, including point of care ultrasound (POCUS), 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.

1. 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 publication² has described additional important and distinctive COVID-19 chest-imaging features. These include the following, seen on both plain chest radiographs and CT:

- 1.1. 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 infarcts². 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.)

2. 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 (NSIP), and described with lung contusions, pulmonary alveolar proteinosis, SARS, and pneumocystis jirovecii infection ¹¹. (The specificity of this finding depends on the prior probability of COVID based on molecular detection via 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.)

3. Additional Annotation to Images

The paper's images show the following (currently unannotated) features.

- Subpleural sparing: Fig. 4B [just under arrow marked as GGO] and 7C/F.
- Hampton's Humps: Figs 2E/F, 4B (marked as consolidation), 4C, and 7A (larger, but fewer, in the right lung than left lung)
- Westermark sign: Fig 2F.
- Pericardial air: Fig. 2C.
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4. Amplified Discussion of Cardiovascular affection by COVID -

Distribution of Cardiovascular ACE2 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 (TMPRSS2) 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 ⁷ for

prognostication of in-hospital mortality is now mandated in most clinical protocols to differentiate mild from severe COVID-19²², especially when coupled with thrombocytopenia⁸. 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.

5. Role of Cardiac & Thoracic MRI

While the authors correctly note that Cardiac 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 injury²¹. (Figure 1)
- Among post-discharge patients, approximately 10% complain of palpitations, with half of these having ongoing chest pain 6 months after discharge¹⁵.
- Dilated Cardiomyopathy is a known complication of COVID cardiac injury²⁷. (Fig 2)
- 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 dose²⁸.
- A recent report implicates the booster dose of the COVID-19 vaccine for acute myocarditis too²⁹.
- In infants and children with COVID 19 reports of coronary artery aneurysms (CAAs), including giant CAAs are gathering momentum²³⁻²⁶; and Cardiac MR/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 thrombosis²⁴. Management includes cardiac support, immunomodulatory agents, and anticoagulation²⁶. Richardson et al²⁴ stated that COVID-19 infection in infants can lead to rapidly progressing CAAs even in the absence of cardiac dysfunction; and that in contradistinction to published reports, haemodynamic instability, ventricular dysfunction, myocardial ischaemia or myopericarditis may not be evident in such cases. Long-term follow-up is required due to the unclear prognosis and risk of progression of cardiac manifestations²⁶.

Coronary arteries should therefore be thoroughly assessed in patients presenting with MIS-C symptoms.²⁵ For its non-ionizing radiation nature MR 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 3).

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 in the imaging of COVID-19 infection, thoracic MRI can also be used as an alternative diagnostic tool, due to its advantages³², especially for patients in whom exposure to ionizing radiation should be avoided; particularly in children and during pregnancy where pulmonary MRI may represent a suitable alternative to chest CT³³. 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 al³⁴ have suggested that during the current pandemic, the portions of the lungs imaged on cardiac or abdominal MRI should be carefully evaluated to promote the identification and isolation of unexpected cases of COVID-19, thereby curbing further spread of the disease. 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 coloured 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/MR 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.

6. Role of 18-Fluorodeoxyglucose (FDG) PET

The authors' suggestion of using 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 patients with concomitant malignancies and other states of immunocompromise, where prompt recognition of infection and early initiation of supportive care is crucial to maximizing outcomes and improving survivability³³.

7. Role Optical , Thermal Imaging & other Remote Patient Monitoring Devices :

Lukose et al³⁷ stated that the presently popular approach of a collection of samples using the nasopharyngeal swab method and subsequent detection of RNA using the real-time polymerase chain reaction suffers from false-positive results and a longer diagnostic time scale; 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 have given a comprehensive review of the various photonics technologies employed for virus detection, particularly 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 al³⁸ have reported a proof of concept of Optical imaging spectroscopy for rapid, primary screening of SARS-CoV-2. A study by Shah et al³⁹ found that home pulse oximetry monitoring identified the need for hospitalization in initially non-severe COVID-19 patients when a cut-off of SpO₂ 92% was used and that home SpO₂ monitoring also reduced unnecessary Emergency Department (ED) revisits. McKay et al⁴⁰ 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 (IRT) has been considered a gold standard method for screening febrile individuals at the time of pandemics since the severe acute respiratory syndrome (SARS) outbreak in 2003. Khaskari et al⁴³ showed that in addition to an elevated body temperature, a patient with COVID-19 experiences a change in tissue oxygenation, cardiovascular, and respiratory functions. Hence, there is an urgent need to develop a new technique capable of rapidly screening all these signals and integrating the measured parameters into new metrics for early detection of viral infections. In their opinion, keeping the advent of wireless technologies in mind, the development of sensors with point-of-care home-accessible capabilities to manage the growing number of infected patients staying in home quarantine, will be very useful and 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). Optical technologies already account for a large portion of RPM platforms, with a good potential for future growth and the biomedical optics community has a potentially large role to play in developing, testing, and commercializing new wearable and RPM technologies to meet the changing healthcare and research landscape in the COVID-19 era and beyond⁴⁴.

Various other ingenious methods/modalities have been used for early detection/screening for COVID 19. These include smartwatches⁴⁵, smart phones and other Intelligent Edge devices. Mishra et al⁴⁵ 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 al⁴⁶ stated that when used in conjunction with predictive platforms, users of wearable devices could be alerted when changes in their metrics match those associated with 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 which 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 al⁴⁷ in their paper titled '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 artificial intelligence 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.

8. Artificial Intelligence (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 accuracy⁴⁸. While the application of AI to medical images for malignancies and other diseases has been under development for decades, the recent COVID-19 pandemic compressed the need/development/training, and the testing of AI algorithms, all within a timespan of less than two years⁴⁹. These helped radiologists and

physicians perform rapid diagnosis, especially when the healthcare system was overloaded⁵⁰. The benefits including for management, were obvious, but limitations such as limited datasets (both in terms of quantity and quality), inaccurate implementations of training and testing procedures, and use of inappropriate performance metrics needed to be dealt with. The above limitations can be overcome by the utilisation of Federated Learning^{48, 51, 52}.

The technique of Federated Learning (FL) was originally pioneered by Google⁵³ as an application of their well-known MapReduce algorithm⁵⁴ 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 possible⁵¹.

If AI is to make an even greater impact Merchant et al⁴⁸ 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 convergence of experts from multiple disciplines including clinicians, medical physicists, imaging scientists, computer scientists, and informatics experts for solving the challenges of the COVID-19 pandemic, specifically, artificial intelligence (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 whole of the transitions more

than the sum of each discipline, for confronting an emergency like the COVID-19 pandemic. AI has been used in multiple imaging fields for COVID 19 imaging.

Manokaran et al⁵⁶ model based on DenseNet201 was able to achieve an accuracy of 94% in detecting COVID-19 and an overall accuracy of 92.19%. The model was able to achieve an 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 al⁵⁷ proposed a solution to automatically classify COVID-19 cases in chest x-ray images wherein the ResNet-101 architecture was adopted as the main network with more than 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 al⁵⁸ stated that separable SVRNet and separable SVDNet models greatly reduce the number of parameters, while improving the accuracy and increasing the operating speed.

Li et al⁵⁰ utilized a large CT database (1112 patients) provided by China Consortium of Chest CT Image Investigation (CC-CCII), and investigated multiple solutions in detecting COVID-19 and distinguishing it from other common pneumonia (CP) 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 al⁵⁹ investigated the potential of deep transfer learning to predict COVID-19 infection using chest computed tomography (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 CNNs with transfer learning to predict COVID-19 in both chest CT and x-ray images. They concluded that this method could help radiologists increase the accuracy of their diagnosis and increase overall efficiency in COVID-19 management.

Cho et al⁶⁰ performed quantitative CT analysis on Chest CT images using supervised machine-learning to measure regional ground glass opacities (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 al⁶¹ 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 separation between patients who received steroids and those who did not and concluded that their cascade deep learning method has strong clinical potential for informing clinical decision-making and monitoring 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 (IOT) but 'Intelligent Edge' devices commonplace⁶²]; 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 dreams⁵¹. 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). 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 locations⁶³. Medical Imaging including COVID 19 / other pandemic imaging & Artificial Intelligence will never be the same again, in the era of Quantum Computing and Quantum Artificial Intelligence, Medical Imaging & Healthcare will reach stratospheric levels, and beyond⁴⁷.

8. Correction: Pg. 260, “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 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.

References:

1. Pal A, Ali A, Young TR, et al. Comprehensive literature review on the radiographic findings, imaging modalities, and the role of radiology in the COVID-19 pandemic. *World J Radiol* 2021; 13: 258-282. 2021/10/12. DOI: 10.4329/wjr.v13.i9.258.
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