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RESEARCH ARTICLE

Quantitative Progression analysis of Post-Acute Sequelae of COVID-19, Pulmonary Fibrosis (PASC-PF) and Artificial Intelligence driven CT scoring of Lung involvement in Covid-19 infection using HRCT-Chest images

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ABSTRACT

Covid-19 is a contagious respiratory disease caused by SARS-COV-2 coronavirus, continue to spread across the world since Jan'2020. Covid-19 can be diagnosed by Nucleic Acid Testing, Antigens Test and Serology Tests or by Digitized Medical Imaging tools like X-ray and High-Resolution Computed Tomography (HRCT)-Chest images. Advanced computational technologies like Artificial Intelligence (AI) - Deep Learning models can assist the radiologist in quantitative, accurate, infection severity and consistent diagnosis, by training the computational system to learn the features of Covid-19 by feeding practitioner's annotated CT images. Quantitative HRCT assessment of severity of COVID-19 infection was widely appreciated by medical fraternity, various government administrations across the world during the early phase of infection. During digitized HRCT-Chest images analysis, the typical features of COVID-19 like bilateral peripheral Ground Glass Opacities (GGO) and/or consolidation, predominantly involving the lower lobes of lung are analyzed. Bilateral peripheral rounded patchy ground glass opacities have been analyzed. HRCT images analysis helps to identify pre-dominant patterns of lung abnormalities like unilateral, multifocal and peripherally GGOs. Most patients make a complete recovery, few of them continue to experience sequalae long after they recover from the acute infection. The most common sequalae symptoms reported were lost of taste or smell, fatigue, and shortness of breath. This constellation of sequalae symptoms, is called Post-Acute Sequelae of COVID-19 (PASC). A subset of patients recovering from infection continue to have persistent respiratory symptoms and chest imaging abnormalities. Our AI-Deep Learning Model is calculating the extent of lung involvement (% of involvement) which is common in the acute phase of infection, was recognized early in the pandemic. While the GGOs and consolidations slowly improved after Covid-19 recovery, fibrosis was seen considerable percentage of patients on follow-up scans after discharge. Results arriving out from our AI model is very much helpful to focus on the post-acute lung disease in COVID-19. Our Deep Learning model analytics on quantitative HRCT metrics of fibrotic lung disease quickly facilitate a role in the evaluation of post covid symptoms, lung fibrotic changes or pulmonary fibrosis.

Keywords: Covid-19, CT-Images, Lung involvement in Covid-19 images, Post-Acute Sequelae of COVID-19 (PASC), Pulmonary Fibrosis (PF), PASC-PF

Introduction

Covid-19 is an infectious respiratory disease caused by a new corona virus called SARS-COV-2. This SARS-COV-2 virus is an RNA virus like flu and measles which prone to changes and mutations similar herpes, small box and Human PapillomaVirus (HPV) DNA viruses.[1] The Covid-19 disease diagnostics is broadly done under two categories, either through laboratory base approaches such as nucleic acid testing, antigens test and serology (antibody) tests or through medical imaging tools such as X-ray and computed tomography.[2]

As, this disease is fast spreadable, early identification of Covid-19 helps to isolate people from the infected and to reduce the disease spread. Despite RT-PCR remains the primary and gold standard for Covid-19 diagnosing, diagnostics using chest CT scans as a simpler, quicker and more reliable way in Covid-19 diagnostics. Thus, CT scan will help the early detection of Covid-19 quickly. In the place of RT-PCR test kits shortage, CT-Scan can be used as an alternative for screening and diagnosing of Covid-19. Covid-19 disease affects many organs like heart, blood vessels and lungs. The ACE2 (Angio tension-Converting Enzyme2) surface receptor are found in alveoli (Tiny air sacs which takes oxygen from our breath) of human lungs. Covid-19 virus binds with this ACE2 and makes breathing difficult. CT scan helps to identify this kind of abnormality. Various study findings shown that circulating miRNA-21 quantification provides critical insights for elucidating Transforming Growth Factor Beta (TGF-β) proteins mediated pulmonary remodeling which involved in fibrosis developments.[3] These measures will help us to achieve better clinical outcome in real-time with high diagnostic accuracy. Hence, by modulating miRNA-21 and their targets, it may be possible to explore better diagnostic, prognostic and therapeutic approaches that
may influence post-COVID complications in the future.

Various research studies show that the patients who recovered after acute COVID-19 illness continue to experience various signs and symptoms at variable timeframes. The most commonly reported sequalae symptoms were lost of taste or smell, fatigue, and shortness of breath. This post covid, constellation of sequalae symptoms, is called Post-Acute Sequelae of COVID-19 (PASC).

Digitized HRCT-scan images analysis helps us to identify Unilateral, Multifocal and Peripherally Ground Glass Opacities (GGO), which are predominant patterns of lung abnormalities. GGOs are Covid-19's early infection sign while it is pulmonary consolidation for later stage. Due to disease load in the vast population, radiologists find manual annotations of lung infections is very tedious and time-consuming task, which is getting influenced by their bias decision and clinical experiences.

Technological advancements in the computational field, especially in Artificial Intelligence (AI)-Deep Learning (DL) models will assist the radiologist in quantitative, accurate, infection severity and consistent diagnosis. These technologies facilitate a faster and accurate identification of Covid-19's typical features like Bilateral Peripheral GGO and/or consolidation, which are predominantly involving the lower lobes of lung. DL models learns these Covid-19 imaging features from the expert (radiologist) marked Covid-19 CT images and automatically predicts the Covid-19 regions by using their learnings.

Narhes and Shervin et.al.[4] proposed a U-Net DL model for Covid-19 segmentation. They used 929 images from medseg.si of size 630*630 and the model produces a dice score of 86% and average precision of .94. Athanasis and Eftychios et.al.[5] proposed another CT segmentation customized U-Net DL which is completely built with convolutional layers, dense layers and a FCN8 network. The authors' model consists of used 939 cross sectional CT-images of size 630*630 from Radiopaedia.[6] The authors stated that their custom U-Net DL model produced more coarse boundaries than regular U-net which produces smoother and smaller than that of the original annotated area.

Arnab kumar Mishra,Sujit kumar Das et.al[7] explored number of popularly used DL models like VGG16, Inception V3, Resnet 50 and Densenet using publicly available datasets.[8] The authors model improved predictions efficiency of the baseline model with decision fusion approach with a F1 accuracy of .883.

Qingsen Yan,BO Wang et.al[9] designed the Covid-segNet DL model has a Feature variation (FV) method automatically adjusts the confusing boundaries of Covid-19 region and thus enhances the annotated images features.

Amine Amyar,Romain modzelewski et.al[10] proposed an automatic CT screening tool with multitask learning model having three tasks classification, segmentation and image feature reconstruction. The proposed CT screening model produces .88 dice coefficient for segmentation task and higher than 97% area under the ROC curve for the classification task.

As Dilibag singh,vijay kumar et.al[11] reported that among various chest CT Covid-19 images classifications like CNN, ANN, ANFIS methodologies, CNN is the best except hyper parameters tuning parameter. Deng-pingfan, Tao Zhou et.al[12] developed, Inf-Net, an automatic Covid-19 regions detection model. This model used a semi-supervised framework, which requires minimum number of annotated images for training. This model aggregates high level features by using parallel partial decoders.

As Han X et.al[13] reported that approximately one third of participants who recovered from severe Covid-19 developed lung fibrotic-like changes within 6 months of their recovery. The authors also reported those older than 50 years have acute respiratory distress syndrome and higher baseline CT lung involvement score.

This paper discusses about AI-DL Model to calculate the extent of lung involvement (% of involvement). This paper discusses about the role of AI-DL model analytics on quantitative HRCT metrics of fibrotic lung disease to facilitate the evaluation Post-Sequelae of Covid-19 (PASC) symptoms, lung fibrotic changes or pulmonary fibrosis. This paper proposes a DL with multi-diagnostic tasks namely 1. Binary Classification of Covid-19 2. Automatic CT Lung Segmentation and 3. Covid-19 region segmentation on CT images with lung involvement score.

Methods

This paper proposes a DL model with three multi-diagnostic tasks, namely 1. Binary classification of Covid-19 2. Automatic lung segmentation and 3. Covid-19 region segmentation with lung involvement scoring.

For the proposed DL model, the chest CT images are collected from medical segmentation created by Medseg[14] which contains two volumetric CTS with 100 axial CT images from >40 patients with COVID-19. One CTS one with 10 axial volumetric CTS, each volumetric CT axial contains 100 slices of Covid-19 images with masks of size 512*512. Other 9 axial volumetric CTs contains 829 images and masks of size 630*630. All these images are of NIfTI format can be used with python Nibabel packge.[15]

1. Binary classification Task

This diagnostic model predicts positivity of Covid-19 from the CT images. All the given CT images are resized into the same size of 630*630 by using nearest neighbor interpolation the CT images. All the images in the dataset are divided into 585, 65 and 275 for training, validation and testing.

This diagnostic model used VGG16[16] and Resnet-50[17] deep learning architecture, Convolutional Neural Networks (CNNs) to classify Positivity and Negativity of Covid-19 on the CT image. VGG16 is a CNN consisting of different blocks with convolutional layer forward by max pooling and fully connected layers (dense layers) at the backend with output layer at the end. During initial stage convolutional layers learn the high-level features and the backend dense layers learn low level features. Model size is around 528 MB and has 138,359,544 parameters. The architecture of the VGG-16 model is illustrated in Figure 1.

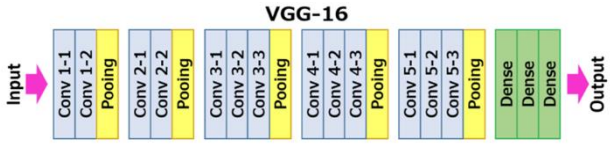

Fig. 1. Architecture of VGG16

Another CNN Resnet-50 uses 50 layers deep with skip connections to learn low level features. Resnet-50 architecture and its skip connections are illustrated in Figure 2.

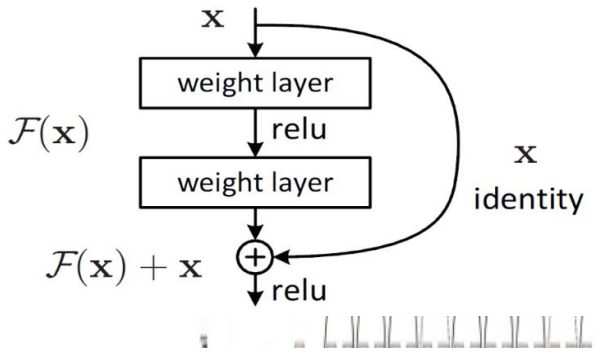

Fig. 2. Resnet Architecture and Skip connections

2. Lung Detection Model

This diagnostics model automatically identifies the lung region in the CT-images. The U-net[18-19] DL model is used for semantic segmentation. In U-net model the input images pass through multiple stages of convolutional and pooling to reduces the height and width of image while passing in deep h after each convolution in down sampling. Subsequently model fully convoluted and produce image mask through multiple stages of up sampling. The architecture of the U-Net CNN is illustrated in Figure 3.

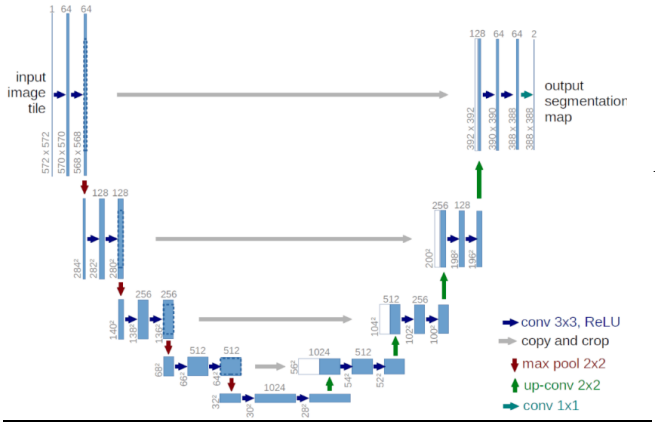

Fig. 3. Architecture of U-Net Model

3. Covid-19 Region Segmentation

This diagnostics model segments and identifies the Covid-19 region in the lung CT image. This diagnostic model is implemented using U-Net CNN with the same modified loss function which segments the Covid-19 region in CT images. This diagnostics model uses 373 resized (624*624) Covid-19 positive marked images with the training, testing and validation ratio of 240:75:58 respectively. Publicly available dataset collections medRxvv[20], bioRxiv[21] and pyMuPDF[22] are used by this model to predict Covid-19 region.

Results

The results section details out results obtained from all three diagnostics tasks as proposed in the model.

A. Binary Classification Model

The classification diagnostic task was performed using two CNN models namely, VGG16, RESNET50 models and each model with two different learning rates. The evaluation metrics like Learning Rate, Accuracy, Precision, Recall and F1 Score are listed out in the table 1.

Table 1. Evaluation Metrics of various CNN Models

Model	Learning Rate (Adam)	Accuracy	Precision	Recall	F1 Score
VGG16	0.001	45.87	45.8	1.00	62.8
RESNET50	0.001	94.24	92.42	95.31	93.85
VGG16	0.0001	97.132	96.15	97.66	96.90
RESNET50	0.0001	97.132	96.88	96.88	96.88

The confusion matrix for the diagnostics CNN models are listed out in Table 2 and their training times are reported in Table 3.

Table 2. Confusion Matrix

Model	Learning Rate	TN	FP	FN	RP
VGG16	0.001	0	0	151	128
RESNET50	0.001	141	10	6	122
VGG16	0.0001	146	5	3	125
RESNET50	0.0001	145	6	4	124

Table 3. Training Time

Model	Time (Approx)	Epochs
VGG16	1 Hour 30 Mins	100
RESNET50	2 Hour 30 Mins	100

All the models were trained using NVidia DGX Station, having 4xTesla V100 cores with 4x80GB GPU RAM, 512 GB CPU RAM with 12 TB hard disk.

Actual predicted results against the practitioners ground truth were given using VGG-16 Model, are illustrated in the Figure 4.

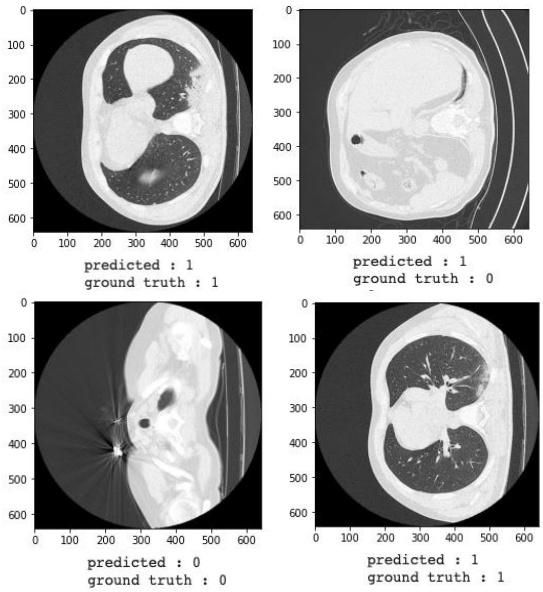

Fig.4. Classification prediction results against ground truth using VGG-16

Actual, predicted results against the practitioners ground truth were given using the Resnet50 Model, are illustrated in Figure 5.

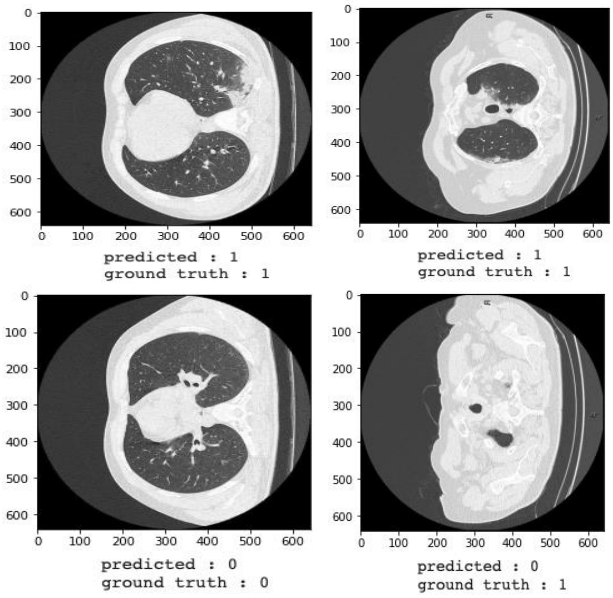

Fig.5. Classification prediction results against ground truth using Resnet50

In the Binary Classification diagnostics task has achieved F1 scores 96.90, 96.88 for VGG-16 network and Resnet50 network respectively.

A. Lung Detection Model

With the ratio of 450:214:49 images in Training, Testing and Validation respectively, the lung detection model used a modified loss function, combined the dice loss and binary cross entropy. This model produces an accuracy of 98.2, specificity 99.83, sensitivity 98.3, dice coefficient 97.21 and IOU 95.44. Lung segmentation predicted results with practitioners ground truth mask as illustrated in Figure 6.

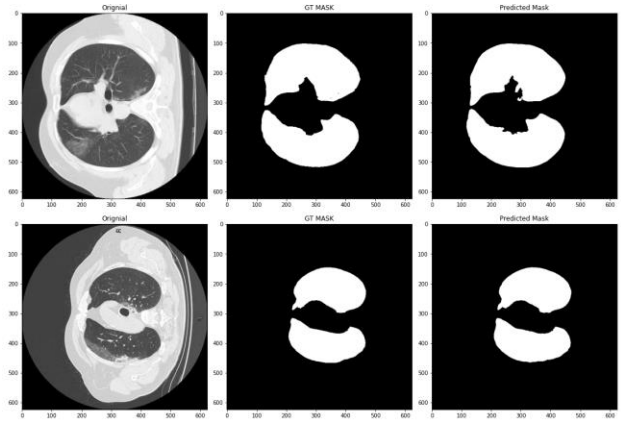

Fig.6. Lung segmentation prediction results against the ground truth mask.

c. Covid-19 Region Segmentation

This diagnostic model, which segment and predict the actual Covid-19 infected region in the lung. This model produced evaluation parameters: accuracy 99.4, specificity 99.5, sensitivity 80.83, dice coefficient 72.4 and IOU 61.59. The actual detected Covid-19 region using this model as illustrated in the figure 7.

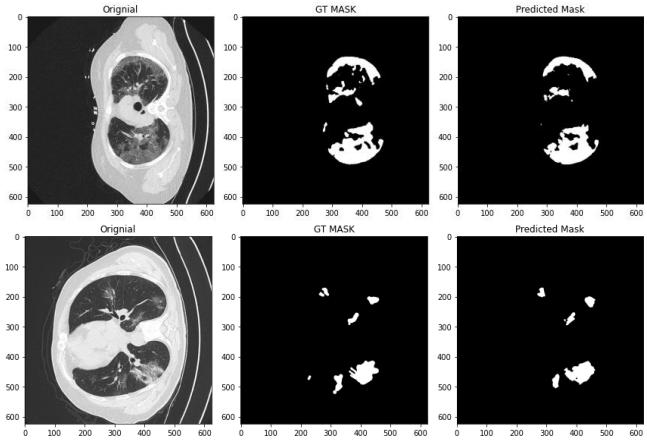

Fig.7. Covid region segmentation prediction results against the ground truth mask using the U-Net.

Discussion

The infectious disease Covid-19 spreads globally for the last three years and the death rate increases at an exponential rate. Shortage of the RT-PCR toolkit forcing us to use digitized HRCT images analysis as an alternative diagnosing model for detecting early detection of Covid-19. The radiologists workload has been substantially increased due to increase in CT images bandwidth and also the new Covid-19 virus diagnostics consumes a lot of time. This paper proposes an AI-DL driven diagnostics model having three automatic DL diagnostics tasks such as binary classification of Covid-19 images, detection of lungs region on HRCT images and Covid-19 region identification on HRCT images. Subsequently, calculate the visual CT severity scores, based on degree of lung involvement in Covid-19 infection.

As Francone M, et.al[23] stated that the main hallmark of COVID-19 pneumonia, is the presence of bilateral GGOs with or without consolidative areas, with a predominant peripheral, lower lobes, and posterior anatomic distribution.

As Joshua J, et.al[24] reported that in the Covid-19 infection's acute phase, lung involvement is common. In the acute phase, lung involvement extent associated with underlying systemic inflammation and showing signs of worse outcome.

The constellation of symptoms which are initially referred as "long COVID," is now stated as Post-Acute Sequelae of COVID-19 (PASC). Recovery period from Covid-19 infection varies across the patients, globally. Most of them make complete recovery, remaining continue to experience sequalae even after their recovery with mild to severe symptoms. Havervall S, et.al[25] reported in their study that 26% of health care workers experienced to have moderate to severe symptoms for 2 months and around 15% experienced to have moderate to severe symptoms for 8 months. And the most common symptoms experienced were loss of taste or smell, fatigue, and shortness of breath.

In their study, Ooi GCKP, et.al[26] reported that in they noticed reticular abnormalities in 2 weeks, wherein CT abnormalities were most severe in their SARS-CoV patients outbreak dataset. The authors have used the dataset from Cherry JD and Krogstad P's[27] 2003-SARS-CoV outbreak study which has 8000 confirmed cases with mortality rate of 9%.

Antonio GE, et.al[28] found that fibrosis was seen with 50-60% of patients during follow-yp scans after their recovery and discharge. Whereas, the GGOs and consolidations in their scans were slowly improved. In another study, Antonio GW, et.al[29] found that fibrosis was more common with the elderly population, patients with a longer length of stay and those with a higher lactate dehydrogenase in the acute phase. Chan KSZJ, et.al[30] reported that fibrosis was found with patients who has notable exercise intolerance after recovery.

Along with radiographic imaging abnormalities, most of the patients tend to have accompanying symptoms like breathlessness with or without cough and abnormalities on lung physiology. However, it is reported that a quite a few of patients experienced to have symptoms with lung involvement and without imaging abnormalities. Also, quite a few patients experienced to have substantial imaging abnormalities without these accompanying symptoms.

However, for the ideal role of quantitative CT to assess PASC-PF can be established by developing distinct metrics to differentiate GGO and fibrotic appearing abnormality. Humphries SM, et.al[31-33] have reported that well known data-driven deep learning technique textural analysis for chronic fibrotic lung disease found a correlation with visually estimated fibrosis and with physiologic impairment. In another study, Humphries SM, et.al[34-35] stated that these deep learning based textural analysis can help us disease progression prediction. A subset of patients who recovered with this acute infection tend to have persistent respiratory symptoms and chest imaging abnormalities. And there is no widely accepted Covid-19 prognostic biomarker to identify patients needing immediate medical attention and to estimate their associated mortality rate. So clinical CT imaging findings, prediction of disease progression and its clinical-lab findings may facilitate practitioners in triaging patients and to timely establish treatment. A quantitative metrics, a measure like CT scoring may help to stratify patient's risk and disease predict and progression.

Globally, pulmonary Fibrosis (PF) is a frequently reported COVID-19 sequela in which the exact prevalence and risk factors are need to ascertained. Currently there is no systematic literature review on Post-Acute Sequelae of COVID-19 (PASC), Pulmonary Fibrosis (PASC-PF). The most frequent CT findings within the lung abnormalities are Parenchymal Bands, Interlobular Septal Thickening and Coarse Reticulations. As Bnar J, et.al[36] reported that around 44.9% of COVID-19 survivors appear to have developed PF and the COVID-19 severity factors were considerably associated with PASC-PF development. Authors reported that PF was 2.88 times more prevalent in patients with Chronic Obstructive Pulmonary Disease (COPD) and PF was 0.51, 0.69 times less prevalent with diabetes and hypertension patients respectively.

The most frequent CT findings in Covid-19 are GGO, Crazy-Paving Pattern (GGOs with superimposed inter- and intralobular Septal Thickening) and consolidation. Feng Pan et.al[37] have worked out a Covid-19 staging system, Stage-1 to Stage-4 based on chest CT scans and the degree of lung involvement. In each stage group, the lower lobes were more inclined to be involved higher CT scores. The authors reported that the CT scores of bilateral lower lobes had significant differences than with corresponding upper and middle lobes in stage 3 and 4.

In their quantitative metrics analysis of degree of lung involvement Ali, R.M.M. and Ghonimy, M.B.I[26] have worked out on a visually scored scale for the degree of lung infection. The authors divided the lung into five lung lobes and each lobe infection was visually scored based on involvement, starting with scale-0 showing no involvement, stage-1 with 5% involvement, stage-2 with 25%, stage-3 with 26-49%, stage-4 with 50-75% and stage-5 showing

more than 75% involvement. The aggregated CT score was the addition of all individual lobar scores ranging from 0 (no involvement) and to 25 (maximum involvement)

The proposed model in this paper does an automatic calculation of these CT scores based on degree of lung involvement, after performing all the three diagnostic tasks and validated by practitioners, subsequently, practitioners deduce a quantitative measure and metrics of degree of lung involvement on the arrived digitized HRCT image findings.

Conclusion

A number of literature studies show that progressive fibrotic lung disease is one of the potential COVID-19 pulmonary pneumonia consequences. And PASC-PF is one of the most worrying long-term complications over next few years. Also, PF is closely associated with non-reversible lung dysfunction. The PASC-PF, long-term lung changes are still not completely understood. With the technological advancements like AI-DL analysis on clinical HRCT images will facilitate and enhance our disease prediction systems. Also the early detection of serious complication for the patients giving a chance for early introduction of anti-fibrotic drugs. Having quantitative measure, metrics like CT Scoring system will provide a logical reasoning and improves the practitioner's confidence in analytics. AI-DL driven automatic CT scoring systems leverage the computers' non-tiring behaviour to deduce consistent, accurate quantitative measure, metrics will encourage the research fraternity to do more concrete research with quantitative measures in precious life-saving field.

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