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Artificial Intelligence Empowers Radiologists to Differentiate Pneumonia Induced by COVID-19 versus Influenza Viruses

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ABSTRACT

Background: Given the current pandemic, differentiation between pneumonia induced by COVID-19 or influenza viruses is of utmost clinical significance in the patients' management. For this purpose, this study was conducted to develop sensitive artificial intelligence (AI) models to assist radiologists to decisively differentiate pneumonia due to COVID-19 versus influenza viruses. **Methods:** Cross sectional chest CT images (N=12744) from well-evaluated cases of pneumonias induced by COVID-19 or H1N1 Influenza viruses, and normal individuals were collected. We examined the computer tomographic (CT) chest images from 137 individuals. Various pre-trained convolutional neural network models, such as ResNet-50, InceptionV3, Wide ResNet, SqueezNet, VGG 16 and VGG 19 were fine-tuned on our datasets. The datasets were used for training (60%), validation (20%), and testing (20%) of the final models. Also, the predictive power and means of precision and recall were determined for each model. **Results:** Fine-tuned *ResNet-50* model differentiated the pneumonia due to COVID-19 or H1N1 influenza virus with accuracies of 96.7% and 92%, respectively This model outperformed all others, i.e., InceptionV3, Wide ResNet, SqueezNet, VGG 16 and VGG 19. **Conclusion:** Fine-tuned and pre-trained image classifying models of AI enable radiologists to reliably differentiate the pneumonia induced by COVID-19 versus H1N1 influenza virus. For this purpose, *ResNet-50* followed by *InceptionV3* models proved more promising than other AI models. Also in the supplements, we share the source codes and our fine-tuned models for use by researchers and clinicians globally toward the critical task of image differentiation of patients infected with COVID-19 versus H1N1 Influenza viruses.

Keywords: Artificial Intelligence, COVID-19 virus, Diagnostic Imaging, Neural network, Radiographic image, Viral pneumonia.

1. INTRODUCTION

The differentiation between pneumonia induced by either COVID-19 or H1N1 influenza virus is complicated. This is because there is a substantial overlap between the clinical manifestations (1-3). Fever, cough, expectoration, and dyspnea are the main manifestations of both pneumonias (2). Other clinical presentations including headache, sore throat, chest pain, fatigue, myalgia, nausea, vomiting, and diarrhea are also common in both infections (1, 2). Coughs and expectoration have been reported more commonly in H1N1 flu than in COVID-19 infection (3). However, the prevalence of other clinical manifestations is similar between the two conditions. Also, there is a substantial overlap in the laboratory findings of the two pneumonias (4). Lymphopenia, elevated C-reactive protein, and erythrocyte sedimentation rates have been reported in both diseases without significant differences. The serum pro-calcitonin level is also not significantly different between the two conditions (2, 3).

It is unlikely that a vaccine or standard treatment for COVID-19 will become available by Fall or Winter 2020 (5, 6). More importantly, seasonal flu outbreak can exist concurrently with the COVID-19 pandemic (7). Given the current pandemic, differentiation between the two pneu-

monias is critical for the patients' management. Equally importantly, differentiation of COVID-19 versus H1N1 influenza on chest CT images is challenging for the healthcare system without experienced chest radiologists (8).

2. AIM

This study aimed to investigate the feasibility of automated diagnostic techniques, using artificial intelligence (AI) models to analyze chest CT images from patients with COVID-19 versus H1N1 influenza pneumonia. Having such a platform can significantly assist radiologists to differentiate pneumonias efficiently during the Fall and Winter of 2020, when a rise in COVID-19 infection is expected. Following a brief review of literature to better inform the readers, the novel findings of this research will be presented and discussed.

3. LITERATURE REVIEW

3.1. COVID-19 Virus

A new form of respiratory infection was detected in Wuhan city, China, in December 2019. In less than one month, the pathogen was recognized as a novel type of Coronavirus. It was named as "severe acute respiratory syndrome coronavirus 2" (SARS-CoV-2), and the resultant infection was called COVID-19. Despite robust international measures and quarantines in many countries, this infection became a pandemic in less than three months. At the time of writing this paper (late Aug. 2020), about 23 million infections and 800,000 deaths have been reported in 188 countries because of COVID-19 infection (9-12). The SARS-CoV-2 is an enveloped single-stranded RNA virus that attaches to the angiotensin-converting enzyme 2 of the airways with a 3-day duration of infectiousness before the onset of symptoms until the complete clearance of the virus. The incubation time is 2–14 days. No vaccine or standard treatment is available for COVID-19 at this time. It is unknown if the COVID-19 prevalence varies in different seasons (13).

3.2. H1N1 Influenza Virus

Influenza infection is one of the common forms of respiratory viral infection. It has been estimated that each year between 291,000 and 645,000 death happens because of the pneumonia due to influenza virus worldwide (2, 14). There are four types of influenza viruses, i.e., A, B, C, and D. Usually, the seasonal flu is caused by type A or B (15). H1N1 influenza is one of the worst subtypes of the flu infections, which has been the cause of two previous pandemics in 1918 and 2009 with 50 million afflictions and over 280000 deaths, respectively (16, 17). The H1N1 influenza is an enveloped single-stranded RNA virus that attaches to the N-acetyl neuraminic acid components of the alveolar pneumocytes (18). Its delivery to other people occurs via droplets from coughs and sneezes (19). The duration of infectivity is from 1-4 days after incubation to days or weeks of severe manifestations, with the prevalence being usually seasonal. There are several approved vaccines and treatments available for H1N1 influenza virus (18).

3.3. Computer Tomographic Scanning

Currently, few studies have been published on the role of medical imaging for the differentiation of the two viral infections. The burden of COVID-19 on chest CT and radiology, in general, is said to be higher than that of the Influenza A (2). Also, it has been reported that the frequencies of bronchiectasis, pleural effusions, linear and crazy-paving opacities, and vascular enlargements within the pulmonary lesions are different in COVID-19 and in Influenza A pneumonia, which may potentially be used as diagnostic elements for differentiation (18). In another study, the COVID-19 patients showed greater number of rounded opacities and interlobular septal thickenings on their chest CT scans but less pulmonary nodules, tree-in-bud opacities and pleural effusions than those with Influenza A and B pneumonias (20). Even though most CT manifestations of viral infections are nonspecific, the preliminary reports are promising about the role of chest CT images in the differentiation of pneumonias induced by COVID-19 versus those by H1N1 influenza virus (21).

3.4. Reverse Transcription Polymerase Chain Reaction (RT-PCR)

While RT-PCR assay, which is a robust and rapid technique for the sensitive and specific diagnosis of Influenza viruses (22) the same is not true for such analysis of COVID-19. The accuracy of this technique for COVID-19 depends on the sampling time and technique used. In this case, false negative results are frequent in the incubation phase. For instance, the likelihood of false-negative results between one to five days before the initial symptoms is 67% to 100%, respectively (23). Further, PCR may give false negative results in 38% of the patients on the day when the initial symptoms of COVID-19 infection occurs. The false negative results decline to around 20% three to four days after the initial symptoms (23).

4. MATERIALS & METHODS

4.1. Data Collection and Expert Review

The study protocol was approved by the Ethics Committee, School of Medicine, Arak University of Medical Sciences (IRB #: IR.ARAKMU.REC.1398.339). The clinical and CT scan data and images from a total of 111 patients with a diagnosis of either COVID-19 or H1N1 influenza infection were reviewed by both a pulmonologist and a radiologist with 25 and 12 years of clinical experience, respectively. The patients' diagnosis had been established based on the analyses of PCR results and the clinical findings. Similar data were also collected from normal subjects who had been admitted for other reasons but were confirmed to have no COVID-19 or H1N1 influenza infection.

4.2. Inclusion & Exclusion Criteria

The clinical data and chest CT images from 72 patients with a PCR diagnosis of COVID-19 were collected between February and May 2020 from the tertiary medical centers affiliated with Arak University of Medical Sciences, Arak, Iran. Also, similar data and chest CT images from 39 patients with PCR positive H1N1 Influenza induced pneumonia were collected between 2017 and December 2019 from the same medical centers. Data for the Influenza cases were collected before December

AI Model (% pretrained)	Clinical Condition	Accuracy (%)	Precision	Recall	F1 Score	Supplements Data
ResNet50 (20%)	Normal	95.76	0.97	0.96	0.96	1, 2
	Covid-19	96.78	0.97	0.88	0.93	
	H1N1 flu	92.54	0.79	0.88	0.83	
ResNet50 (0%)	Normal	82.5	0.88	0.82	0.85	3, 4
	COVID-19	91.99	0.93	0.74	0.82	
	H1N1 flu	80.3	0.39	0.65	0.49	
ResNet50 (30%)	Normal	94.11	0.98	0.92	0.95	5, 6
	COVID-19	97.17	1.0	0.88	0.93	
	H1N1 flu	91.29	0.69	0.92	0.79	
ResNet50 (40%)	Normal	95.37	0.94	0.98	0.96	7, 8
	COVID-19	96.94	0.97	0.88	0.92	
	H1N1 flu	92.31	0.84	0.83	0.83	
InceptionV3 (20%)	Normal	86.54	0.98	0.82	0.89	9, 10
	COVID-19	96.7	0.98	0.87	0.92	
	H1N1 flu	83.79	0.38	0.88	0.53	
InceptionV3 (30%)	Normal	77.71	1.0	0.71	0.83	11, 12
	COVID-19	96.82	1.0	0.86	0.93	
	H1N1 flu	74.76	0	0	0	
InceptionV3 (0%)	Normal	89.72	0.94	0.89	0.91	13, 14
	COVID-19	95.6	0.97	0.83	0.89	
	H1N1 flu	86.89	0.59	0.82	0.69	
Wide ResNet (20%)	Normal	85.4	0.88	0.86	0.87	15, 16
	COVID-19	95.53	0.86	0.92	0.89	
	H1N1 flu	80.93	0.59	0.60	0.59	
Wide ResNet (0%)	Normal	83.36	0.94	0.80	0.86	17, 18
	COVID-19	96.98	0.97	0.89	0.93	
	H1N1 flu	80.34	0.34	0.65	0.45	
VGG-19 (0%)	Normal	86.73	0.94	0.84	0.89	19, 20
	COVID-19	95.37	0.99	0.81	0.89	
	H1N1 flu	83.67	0.45	0.79	0.57	

Table 1. The performance of the retrained AI models to classify normal chest CT images versus those infected with either COVID-19 or H1N1 influenza virus. Note: AI models are listed in order of their differentiation performance. SqueezeNet and VGG-16 models did not render significant differentiation between the two viruses.

2019 to make sure that there is no concurrent infection of COVID-19 and Influenza. Finally, normal chest CT images were collected from 26 normal subjects who had been admitted to hospitals for other reasons. The chest CT images with poor quality due to motion artifacts and/or chronic lung diseases were excluded.

4.3. Chest CT Images Preparation

All CT scanned images were prepared by the standard chest protocol (MA: 24-40, KVp: 100-110), with axial slices less than 1.5 mm, pitch factor of 0.8 and Matrix at 512 x 512. Using *ImageJ* platform, the grayscale images were converted to RBG format. All slices of COVID-19 and Influenza cohorts were reviewed by the same radiologist. In COVID-19 and H1N1 influenza cohorts, slices without visible pathologies were excluded.

4.4. Training CT Images with AI Models

One out of nine slices from the normal cohort, and one out of four slices from the COVID-19 or H1N1 influenza cohorts were selected and used for training with the AI models. Each axial slice was divided vertically into a right and left hemithorax. Augmentation was also performed at 30 degrees of rotation and 0.2 shift ranges rescaling for width and height. The final labeled images were uploaded onto select pre-trained convoluted neural network (CNN) models for further analyses. Overall, 12744 CT images were used to train the AI models, i.e., 2503 for COVID-19, 3035 for H1N1 influenza, and 7206 for normal cohorts.

4.5. Pre-trained AI Models

The six select models were: *ResNet-50, InceptionV3, Wide ResNet, SqueezNet, VGG 16* and *VGG 19*. Each model was pre-trained on 1000 image classes of *ImageNet* program.

- **ResNet-50:** Four variations were developed in this model at 0%, 20%, 30% and 40% trainability.
- **InceptionV3**: In this model three variations were developed at 0%, 20% and 30% trainability.
- **Other Models:** The other four models (Wide ResNet, SqueezNet, VGG 16 & VGG 19) were developed at 0% and 20% trainability.

Sixty percent of the data were used for training, 20% for validation and 20% for "experiments" to "tests". The training and testing were accomplished on the Deep Learning Studio software (24). The output for each pre-trained model was flattened and fed into a dense layer with three output classes, representing the predicted COVID-19, H1N1 influenza, or normal. The training process was identical in all models, with the following features: Epoch number, 10; Batch size, 32; Loss function, categorical cross entropy; Optimizer, Adam program; Beta-1, 0.9; Beta-2, 0.999; Decay, 0; and Learning rate, 0.001. The accuracy, precision, recall, and F1 score for each AI model were determined, as shown in Table 1.

5. RESULTS

The COVID-19 cohort (N=72) consisted of 38 male and 34 female, with a mean age of 60.9 years old, and with the mean time interval between the initial symptoms and taking the chest CT scan of 4.37 days. The H1N1 influenza cohort (N=39) consisted of 20 males and 19 females, with a mean age of 62.4 year old, and the mean time interval between the initial symptoms and chest CT scanning of 5.41 days.

By our pipe-line design, the *ResNet-50*, *InceptionV3*, *Wide ResNet* with various degrees of trainability, and VGG 19 with 0% trainability were able to capture the useful information and performed well on validation and actual cohort tests. The *ResNet-50* with 20% and 30% trainability had the best performance to differentiate pneumonia induced by COVID-19 versus H1N1 influenza virus. ResNet-50 with 20% trainability diagnosed COVID-19 with accuracy and precision of 96.7% and 97%, respectively. The accuracy and precision of this model to diagnose H1N1 influenza were 92.5% and 79%, respectively. This model achieved the accuracy and precision of 95.7% and 97%, respectively, to diagnose the normal slices of chest CT images. In terms of accuracy, precision, recall and F1 scores, the performance of other models were ranked as follows: InceptionV3 > Wide ResNet > VGG-19. SqueezeNet and VGG-16 models did not render a significant differentiation between the two viruses. The results of the tested models are presented in Table 1.

6. DISCUSSION

The COVID-19 pandemic is now one of the worst challenges the modern medicine has ever encountered (6). The viral infection grew to a pandemic scale in less than three months involving the whole world. It is unlikely that an effective treatment or vaccine would become available in the near future (6). This would be the biggest healthcare challenge in the Fall and Winter of 2020 when a seasonal H1N1 influenza outbreak may occur concurrently with the COVID-19 pandemic (7). There are substantial clinical and laboratory overlaps between the two viral diseases (1). To make things even more complicated, the currently standard PCR test is not enough for a perfect diagnosis of COVID-19 (22, 23). In this context, chest CT imaging plays a critical role (2).

It is generally accepted that chest CT scanning is the critical part of medical diagnostics for respiratory infections (25). In a recent study, the prevalence of bronchiectasis, pleural effusion, linear opacities, crazy-paving sign, vascular enlargement, and pleural thickening were statistically different between COVID-19 and H1N1 influenza infections (2). However, the distribution of lesions, ground-glass and nodular opacities, consolidations, bronchial thickening, lymphadenopathy, pericardial effusion, and air-bronchogram were not statistically different between the two infections (2). Despite these findings, differentiation between Influenza and COVID-19 viruses remains challenging because the CT manifestations of the infections are nonspecific. Making the correct diagnosis would be even more challenging at healthcare facilities without expert chest radiologists (26). Thus using an automated and accurate diagnostic platform to enhance the differentiation, such as the models introduced by this study, can make a significant difference in the patients' management. The AI models would also be a considerable relief to the overloaded healthcare staff, especially in the areas without the technology and expert radiologists.

Recently, many convolutional neural network models have been developed for medical image classification, proven to be clinically promising. These AI models are able to achieve differentiating accuracy better than that by radiology experts in image classification. Nevertheless, a major problem for automated medical imaging is the size of datasets (27). The modern CNN-based AI models, such as those developed in this study, utilize data-hungry algorithms (28). To obtain accuracy and precision better than that achieved by expert clinicians, these models need to be trained with many thousands to one million images (29). In this context, the challenge of processing datasets from millions of medical images has been partially resolved by AI's transfer learning techniques. For this purpose, CNN models are not developed from scratch, rather pre-trained models are utilized. The pre-trained models usually are developed on large *ImageNet* datasets, containing millions of non-medical images (30).

Such pre-trained models are then retrained, i.e., fine-tuned on a small dataset of medical images (27). The idea behind such transfer learning is the fact that basic tasks of image classification, such as edge detection and vertical or horizontal lines can be learned primarily based on the non-medical datasets (29). A similar concept was true in our study. Here, we were able to train CNN models for image classifications with small datasets. Having 137 subjects and 12744 images is considered a small dataset for CNN models of AI (30). In this study, we demonstrated that ResNet-50 and InceptionV3 were high performance CNN models for small medical image data sets, achieving a precision between 97.17% and 100% to differentiate COVID-19 from H1N1 influenza virus. ResNet-50 with 20% trainability achieved the accuracy levels of 96.7%, 92.5% and 95.7%, respectively, to diagnose the COVID-19, H1N1 influenza and normal CT slices. Indeed, such an accurate CT image differentiating model adds a significant value to the daily clinical practice of radiology departments worldwide.

Recently, there have been a few case series of co-infection with COVID-19 and H1N1 influenza viruses (31, 32). Also, it is expected that such cases of co-infections may be encountered more frequently by the end of 2020. Obviously, further research and AI model development will be required to diagnose both COVID-19 and H1N1 influenza viruses in the same infected subject. At this time, it is unclear what would be the differentiation accuracy and the output of our AI models if used for patients with the co-infection. The source code and the trained models are provided in the supplements and can be used by other researchers for further studies on this critical subject.

6.1. Limitations of Study: It must be noted that our diagnostic AI models have been trained on the RBG im-

ages, so grayscale CT images must be converted to RBG format before they are fed onto the models. Also, they work only on axial images. They have been trained on the images of the lung parenchyma, so the neck base and upper abdomen images must be deleted before using our pre-trained AI models. Lastly, for data augmentation, these models have been trained on the right or left hemithorax. Thus for deployment, they must be fed by divided axial slices. The input of the models should be an axial image of each hemithorax in the lung window, and the output would be a prediction of COVID-19, H1N1 influenza or normal hemithorax.

6.2. Key points

- Differentiation between pneumonias induced by COVID-19 or H1N1 influenza virus is a challenging task if it is based only on clinical findings and blood chemistry data.
- The development of automated AI platforms based on convolutional neural networks and transfer learning techniques are feasible to do this task accurately, efficiently and rapidly.
- ResNet-50 and InceptionV3 are the promising pre-trained models developed by this study, which can be used as starting points by clinicians and researchers on this important subject.

7. CONCLUSION

This study demonstrated that the development of an automated diagnostic platform to differentiate COVID-19 from H1N1 Influenza pneumonia or normal chest CTs is feasible with considerable accuracy and speed. Based on our findings, the proposed AI models are preclinical solution for the challenging task of differentiating chest CT images from patients with COVID-19 or H1N1 influenza infection. Our automated models will enhance the efficiency of the radiologists with limited chest imaging experience. The ResNet-50 and InceptionV3 were found to be promising models for this challenging task and are appropriate starting points to develop other automated platforms based on AI models for future clinical and diagnostic purposes.

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