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Impact of Radiological Techniques in the Diagnosis of COVID-19

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Abstract
The outbreak of 2019-nCOV around the globe at an exponential transmission rate has led to the declaration of COVID-2019 as a Public Health Emergency of International Concern (PHEIC) by World Health Organization (WHO). It is caused by severe acute respiratory syndrome leading to lung infection eventually to death. Lung imaging provides insight about the extent of infection and adopt treatment accordingly even though a false positive in standard techniques such as RT-PCR and RAD tests. Hence, this review elaborates on the origin of nCoV-2019 and various radiological techniques to identify the rate of infection. Finally, the role of artificial intelligence in processing the lung images is outlinedalong with the combined effort by the individual, media and healthcare organization to substantially limit the outbreak.

1. Introduction

The emergence and spread of 2019 novel corona virus (2019-nCoV) from the Huanan market in Wuhan city, capital of Hubei province is threatening the globe with new public health crisis [1]. The virus was believed to be originated from the crossover of animal betacorona virus to humans as illustrated in Figure 1. As evident, the samples tested from the seafood market showed positive for 2019-nCoV with >95% homology of bat corona virus and 79% similarity with the severe acute respiratory syndrome coronavirus (SARS-nCoV) [2]. Hence 2019-nCoV exhibited similar clinical characteristics to SARS-nCoV, particularly acute respiratory distress syndrome along with other clinical features including cough, sore throat, fever and breathlessness[3]. The onset of the outbreak was first identified during the 1st week of December 2019 when few cases reported in the Wuhan city with the above mentioned symptoms who had history of visiting the Huanan local market. China notified the outbreak to World Health Organization (WHO) on 31st December 2019 and named as 2019-nCoV after characterizing its etiology through Real-time reverse transcription polymerase chain reaction (RT-PCR) and next-generation sequencing on 7th January 2020. 2019-nCoV envelopes a positive sense RNA that possesses multiple spikes across its surface[4]. It is from the family of Coronaviridae predominately found in birds and mammals (Figure 2) which caused SARS-nCoV during 2002-2003 and Middle East Respiratory Syndrome coronavirus (MERS-CoV) during 2012[5]. Hence these outbreaks have significant similarity in symptoms and differences in the mortality rate and transmission capabilities[6]. The SARS-nCoV outbreak began in China with an international spread to Toronto, Canada with 10% fatality rate (8437 cases and 813 deaths) with an incubation period of 4 days. The MERS-nCoV began in Saudi Arabia with an international spread to South Korea and United States with roughly 35% mortality rate with 5 days incubation period. These cases illustrated a decreasing trend in mortality rate and increasing rate in R_o values[7]. With an R_o value of 2.2, 2019-nCoV is spreading at a rapid pace around the globe in 203 countries as of 3rd April 2020[8]. The pandemic has affected 1,016,258 with 53,256 deaths globally. Meanwhile many people have been quarantined and cured (Figure 3). Moreover, the complication in containing the 2019-nCoV relies on the asymptomatic persons who are potential source of carriers. Therefore handling the current outbreak of public health crisis is not new to the world.

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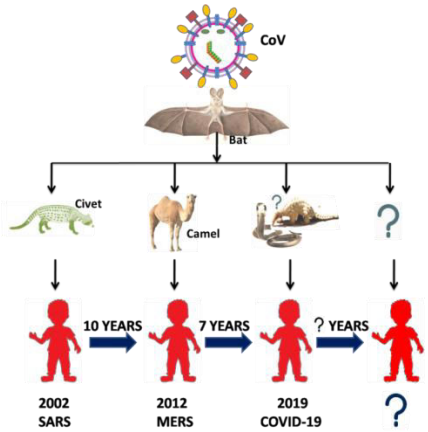

Figure 1: A proposed schematic representation of various phases of crossover of Beta CoV from animals to humans.

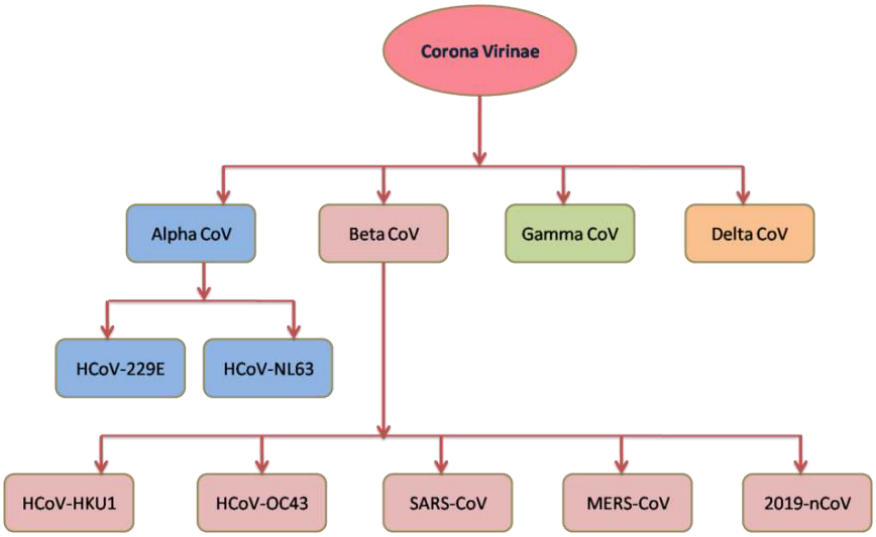

Figure 2: Schematic illustration of Coronavirinae family and its sub-group with the new addition of 2019-nCoV in the Beta CoV.

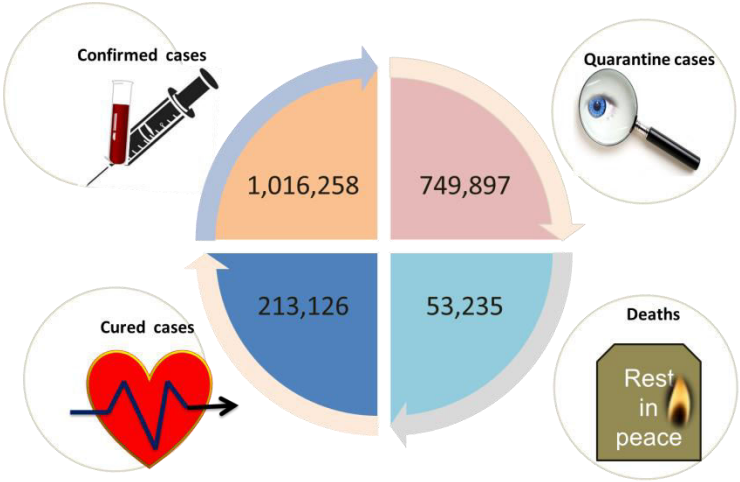

Figure 3: Total number of confirmed, quarantined, cured and death cases around the globe (updated till 03/04/2020).

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2. Methods of Diagnosis

2.1 Standard Methods

2.1.1 Reverse Transcription-Polymerase Chain Reaction (RT-PCR)

The RT-PCR are the first to be developed and widely employed test for novel corona virus and still remains as the primary diagnosis tool. This test detects viral RNA, and the presence of the virus is confirmed by the highly specific positive result. However, the limitation of the tests includes the detection limits, timings of the testing, viral inoculum, sample collection site and the non-uniformity of the sensitivity of the tests. This is based on several gene targets and thus varies in the sensitivity and specificity [9]. It is suggested and recommended the following practices by the IDSA

- RT-PCR testing in symptomatic people, even when the clinical suspicion is low.
- RT-PCR testing in asymptomatic individuals who are suspected to have been exposed to the infection.
- Repeating viral RNA testing when the initial test turns out negative in symptomatic individuals with medium or high level of clinical suspicion
- The collection of samples from nasopharynx,mid turbinate site over the oropharynx or saliva alone.

The detection of virus at the early stages of infection can be aided by the conventional RT-PCR methods and its sensitivity can be increased, when the virus is present at low titer in respiratory secretions [10]. But the concern is due to the presence of RT-PCR inhibitors, false negative results may occur. To prevent such false positive results, care should be taken to prevent the introduction of contaminating viral RNA or already amplified DNA during the preparation of the nucleic acid extracts and amplified reactions [11].

2.1.2 Rapid Antigen Detection (RAD) Test

Rapid Antigen detection test (RAD) detects the viral antigens by immobilizing the novel corona virus antibody that is coated on the device. Within 30 minutes span of time, the results of RAD can be interpreted without any requirement of sophisticated, specialized instrument. Thus RAD test are capable of relaxing the workload in the diagnostic hospitals and laboratories to improve the turns around time [12].

The rapid antigen test device will have two pre-coated lines on the result window called control (C) test (T) lines. An Igγ antibody is coated on Te control (C) region and the test (T) region is coated with mouse monoclonal anti-novel corona virus antibody against novel corona virus antigen. The color particles conjugate with anti- novel corona virus antibody due to the novel corona virus antigen presented in the specimen. Since higher viral loads are anticipated, this rapid antigen test is anticipated to detect early after the symptom onset and has high potential in determining highly contagious individuals [13]. Although they have low analytic sensitivity, these rapid antigens are inexpensive and therefore they are frequently utilized for the detection of infected individuals who are asymptomatic, pre-symptomatic and unknown exposure to novel corona virus. In congregate settings which are places such as long-term care facility, work place, schools and correctional facility, they are proven to be beneficial. When the viral load is higher, such as in the case of early stages of novel corona virus, these rapid antigen tests performed best.The main disadvantages of these tests are the false positive results are high [14]. Therefore lung imaging techniques provide deeper insights on stages of COVID19 and following section discusses about various imaging techniques and staging of COVID19.

2.2 Imaging Methods

2.2.1 Chest X-ray

Although CT imaging is widespread for the use in diagnosis of corona virus, the lack of CT facilities all over the world, inability to control the infection in the CT scan area of the clinic due to the clustering of affected and unaffected patients, and issues related to the transport of the patient to the scan area and decontamination of the scanned area, chest X-ray are preferred for the detection of COVID, in almost many parts of the world. It should also be noted that the decontamination that is required to be done after the scanning may disrupt the radiological services and hence chest radiography is opted to minimize the cross contamination and infection. Additionally, a positive chest x-ray may reduce or neglect the need for a CT scan. This plays a dominant role in the detection when the patients are left with minimal access to RT-PCR tests. COVID pneumonia involves in peripheral lung involvements at high frequencies and are often similar to the other inflammatory dieseases. Greater incidence of the lung peripheral infusion can be readily detected by the chest x-ray which are mutifocal and patchy. Diffuse lung opacticites are found to be coherent with covid as well as other inflammatory diseases of the lung when images by Chest X-rayas shown in Figure 4a [15]. In these detection techniques pleural effusions are found to be prominently rare along with lung cavitaion and pneumothorax. Alveolar rupture can also be detected in several cases where diffuse alveolar damages are observed. In case of additional investigation, more information can be obtained. Retricular, patchy, hazy, irregular ground glass patterns can be observed in the chest X-rays and typical verbiage are

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reported [16]. As the pandemic progress, it is expected for the medical community to rely on chest X-rays for widespread detection of COVID [17].

2.2.2Lung Ultrasound

Although CT imaging is considered as the golden standard for the imaging modality, the use of lung ultrasound in the detection of corona virus has certain advantages and plays a complementary role in the confirmation of the presence. The lung ultrasound is taken with the help of convex and linear probes. Pleural effusion and thickening of pleural lines are the abnormalities that can be observed from the lung ultrasound [18]. The sensitivity of the lung ultrasound are found to be as high as and comparable to that of the chest CT and Radiographies. Decreased alveolar air and high interstitial fluids, that causes the reverberation of the ultra-scan beam, that creates the B-lines and it is one of the most common lung findings. Multiple vertical echogenic reverberation artifacts that are extending from the lung surface are visualized by the B-lines. However, causes such as viral pneumonia, cardiogenic edema, acute respiratory distress syndrome could not be distinguished on a greater significance by the B-lines and thus lower the specificity of Lung ultra sound in the detection of covid. Also the b-lines were found to be present in all the patients, irrespective of the disease and the severity of the patients involved in the study [19]. Similar to how intra lobular and interlobular septa thickening were resulted from the CT analysis, thickened pleural linings were observed in the ultra sound lung scan of the covid patients. However the limitations of the lung ultra sound involves in the inability to find and track the progression of the disease and find out the treatment efficacy. The lung ultrasound scan is incapable of quantitatively evaluating the disease. Also like many other ultra sound techniques, this is also depends on the expertise of the operator and may be ineffective for the inexperienced hands. But the advantages of this technique is that it reduces the number of health care workers required to assist in the detection of the virus and the medical devices exposed to the patient which could further worsen the health condition of the patient by exposing them to the radiations when compared to the radiography techniques [20].

2.2.3MRI

A relatively high percentage (36%) of the symptoms of the covid-19 emanates from the central nervous systems such as change in mental status, headache, cerebrovascular diseases and epilepsy. When a person has higher respiratory disease status, the rates of these neurological symptoms are also found to be higher. These elevated neurological symptoms are in concordance with the neurotropism of the virus [21]. MRI scans shows that the cortical fluid attenuation abnormality in the covid patients accompanied with deep white matter and subcortical abnormalities. Oligoclonal bands were seemed to be unaffected in the patients involved in the study. In another study the MRI did not reveal any abnormalities in the intracranial findings and absence of cortical signal abnormality and infraction in the middle cerebral artery. cytokine storm syndrome is another potential neurological abnormality observed in the corona infected patients. It is observed in the patients who suffered from the acute respiratory syndrome, deep venous thrombosis and pulmonary embolism was found to be predominant. The patients who received intravenous immunoglobin treatment suffered intracranial arterial stroke. These signal abnormalities could detect by the MRI and thus supports in the detection of covid [22]. Due to the breakdown of blood brain barrier and cortical micro hemorrhages which is accompanied by hypoxia that results in the imaging pattern. Image findings can be made plausible by the postictal state, but the involvement of deep white matter have no effect on the changes in the postictal state. Certain autoimmune and encephalitis have a unique pattern of involvement that helps in differentiating the imaging lists. However the non-specificity of imaging pattern makes it harder to establish a pattern to achieve diagnosis based on the MRI scan results. In the absence of distinguished cerebrospinal fluid findings, a causal and effect relationship is slightly hard to establish between the Covid diagnosis and the MRI scan [23].

2.2.4CT

The CT imaging helps in the detection of Covid-19, especially when it is very high in the symptomatic individuals at very high risk. The CT uses a thin section of chest CT. One of the most dominant feature in the patients affected by Covid-19 is it involves in ground glass opacity and consolidation that involves in the bilateral lungs, that are distributed in the peripheral area (Figure 4b). The following aspects are the mainly included features in the recorded chest CT from the covid-19 patient.

- Lesion distribution in the areas such as bilateral lung, central and peripheral area of lung,
- Lobe distribution and the number of lobes involved
- Patterns of the lesions (GGO mixed consolidation, crazy paving pattern, air bronchogram, GGO, consolidation, interlobular septal thickening, pleural effusion, pericardial effusion, adjacent pleura thickening, lymphadenopathy and bronchiectasis).

Patients presenting different scenarios that are early versus advanced stages, asymptomatic versus symptomatic patients, and severe versus non severe situations can correlate their clinical conditions with CT image appearances.

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There are around more than 52 studies that involved the diagnosis of Covid-19 with the help of a CT. The modality that was used in all the imaging technique to diagnosis the covid was CXR [24].

Unilateral and bilateral lung involvement was analyzed in 36 studies and out of which 17 studies reported a more bilateral lung involvement than the unilateral lung involvement in the covid patients. It concluded that the bilateral movements were more frequently observed in severe cases. The rest of the 19 studies did not deliver any details on the involvement of the lung on chest in covid patients, whereas the 8 of the studies were reporting more than two lobes that are involved in all these studies. The chest involvement in the CT images and CXR are revealed by only two of those studies. A significant dominance in the abnormalities or lesions in the central area or central distribution was observed than compared to the peripheral or central peripheral region.The CT images that are most commonly often opacity that are ground glass, which is mainly located in the lower lobes that are accompanied by the consolidation. They are common and non-specific images of lung injury of acute degree and are linked to various infectious and non-infectious inflammatory diseases. The CT findings of these images are vital in identification of pneumonia and that may help in the extended evaluation clinically, especially when other incidental identifications are found during this global pandemic. The triage of the suspected patients in the deployment of the CT is less clear. The sensitivity of the CT scan in detecting the covid are studied by various groups and the clinical findings and epidemiological features are compatible with covid infection and the results have adherence especially when preliminary tests such as RT-PCR testing are supported. It is also suggested that when compared to the threshold of the standard practices, the threshold for a positive result in CT findings are inherently low and this might result in the overestimation of the result's sensitivity. It is estimated that the sensitivity of the tests were as high as 97. The patient population of this study was defined in a unclear manner and it is assumed that the cohort included the patients from the samples had abnormal CT findings when compared to the other normal outpatient people. The study also explored the comparisons of CT in the patients who evolved from negative to positive. CT was used as a binary test with the addition of an undefined and a very low threshold for positivity and due to the bias in selection of the cohort, these factors resulted in the overestimation of sensitivity of CT in covid detection [25].

The specificity and the positive predictive value of any test is based on a standard reference in the laboratory. In RT molecular assay serves as the standard reference. In Rapid tests, the false positives are usually obtained by the presence of any contamination during the collection, transfer and analysis of the sample, and any deviation in setting up the assay for the tests. In CT, the situation is different. Here, a single, unique feature is not associated to the detection of covid. The features such as peripheral and bilateral ground glass opacity that are considered as characteristics to the covid, are reportedly observed in various other conditions which are both infectious and non-infectious. The sensitivity of the CT scans in the detection of the covid in controlled groups. Firstly the group included patients that were affected with only viral pneumonia. None of the patients were infected with other infectious disease. There was no chance of the overlapping of CT with other disease such as organizing pneumonia, lung injury that arises from drug toxicity, cryptogenic causes, radiation treatment, alveolar hemorrhage, pulmonary edema and other interstitial lung diseases. The specificity may be overestimated if the control group has no other aforementioned disease other than pulmonary covid infection. Further, no objectives were mentioned to describe the positive CT examination. In the real world, the practices are slightly different from the laboratory study groups, the diagnosis of the patient affected with cold and fever are quite broad and the other factors falls under significant proportion of the diagnosis. Hence the specificity of the CT in covid diagnosis is much lesser than the reported cases. Further, lack of proper training in diagnosis has been limiting the specificity of the real world applications. The risk of utilizing the CT scans in covid includes over utilization of resources in the hospitals, clustering of both unaffected and affected patients leading to increase in the infection rates [26]. however, at present CT is considered as the best evaluation method for covid diagnosis and as the time progresses, experience in theanalysis of covid is expected to gain by the medical experts.

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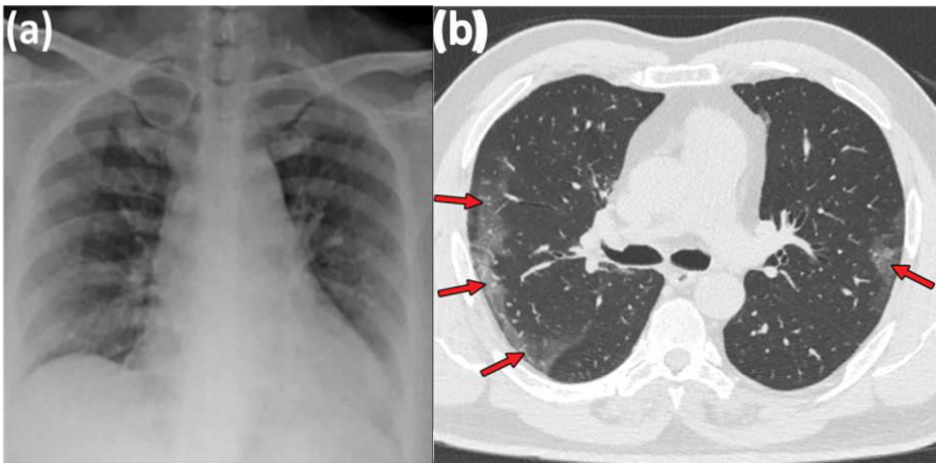

Figure 4: (a) Chest X-Ray [16] and (b) CT images of COVID-19 cases [26].

3. Role of Artificial Intelligence in Processing Lung Images

The estimation of novel corona virus can be done by processing lung images with the help of artificial intelligence. Artificial methods are applied in the area of applications ranging from tracking, containing, and treating viral infection.The crucial fundamental step in the analysis and processing of the detection of the presence of novel corona virus, is the segmentation of the images. The areas such as lesions and lobes of the lung in the image, which are the region of interest is depicted by this technique. This segmented region of interest is used to extract the features. CT scan provides the high quality 3-D images for revealing novel corona virus. U-Net, U-Net ++,VB-Net are the most prominent method for the region of interest in CT scan. But they are not refined for segmentation using an X-Ray image. Segmentation is considered as a fundamental process to investigate the novel corona virus. To extract the features from the X-Ray images, the convolutional neural network method is used [27].

Presently, artificial intelligence is considered as a dynamic tool for the detection and analysis of novel corona virus. This artificial intelligence uses machine learning and deep learning where the machine learning is designed to handle by the people, for determining the structure of the data and the deep learning is designed for the better performance of multi-layered complex neural networks. The accuracy is increased with the increase in number of layers. A section of deep neural networks which consists of multiple layers in the hidden nodes is called deep belief networks. It can be trained with much control to make a classification. It is a four combination of simple, unsupervised works and they serve as a hidden layer of each subnet that is visible to the consecutive layer [28].

The direct learning techniques are employed to enhance the accuracy of prediction by forming models on large scale volumes of data. When it comes to the classification, there are challenges associated with the diagnosis using the person's radiological imaging data that contains layers of steps. In particular, the image classification is done by pre-processing, feature extraction and annotation. The most time consuming step is the annotation and requires and completely dependent on the expertise of the radiologist. The overall accuracy of this method is 80%. AI model performance may turn out to be biased due to lesser sample size from small-scale studies and thus reflects on the data. It is expected that the newer AL studies should utilize data from national and international collaborative COVID-19 repositories. In addition, decentralized AI architecture may be adopted.

Interpretable AI models might allow end users to understand and enhance the performance of the AL model .Researcher and radiologists can accept or decline the recommendations when such models are used as a clinical decision support tool, especially in the diagnosis of novel corona virus. According to various studies, the quantitative descriptive analysis such as variables, data sources, and sample size, AI based model performance was not possible in various selected studies [29].

4. Implementation of Public Health Interventions

Slowing the speed of virus spread is attributed to the measures taken by the Government including the closure of all the medium of transportation (Roadways, Airways, Railways and waterways) to the general public similar to what has been done in China[30]. The week long lockdown period imposed rigorous adherence to home quarantine. All the public gatherings and events were called-off along with the closure of schools and universities. Moreover, people venting out for the purchase of essential commodities were taken care by providing subsidies to the commodities and door step delivery each alternative day. Government and private hospitals are resourceful to tackle

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any number of COVID-19 cases also by converting train coaches as an emergency ward. Furthermore, online seminars and presentation for the task force and healthcare workers were frequently conducted for the identification and treatment of patients with suspected or confirmed COVID-19 cases by the guidelines provided by ICMR[31]. As 2019-nCoV is not aware of national border neighboring countries pulled in an immediate relief fund among them. Similarly, it is the responsibility of the individual to voluntarily report to the healthcare organization or self-quarantine in terms of symptoms or contact with COVID-19 cases[32, 33]. Meanwhile, media houses are encouraged to be responsible for broadcasting the latest update on COVID-19 with transparency[34]. The labeling of rumors and fake news floating in various social media as "Infodemic" by WHO has led to the initiation of "myth busters" webpage to avoid unnecessary commotion and panic (Figure 5).These combined measures by the individual, media houses and government healthcare organizationswere partially successful and have resulted in the delay of COVID-19 spread in India even though it continue to rise globally. We thank all the healthcare providers, researchers, scientists and all the officials for rendering their service in one or the other way to the COVID-19 struck community.

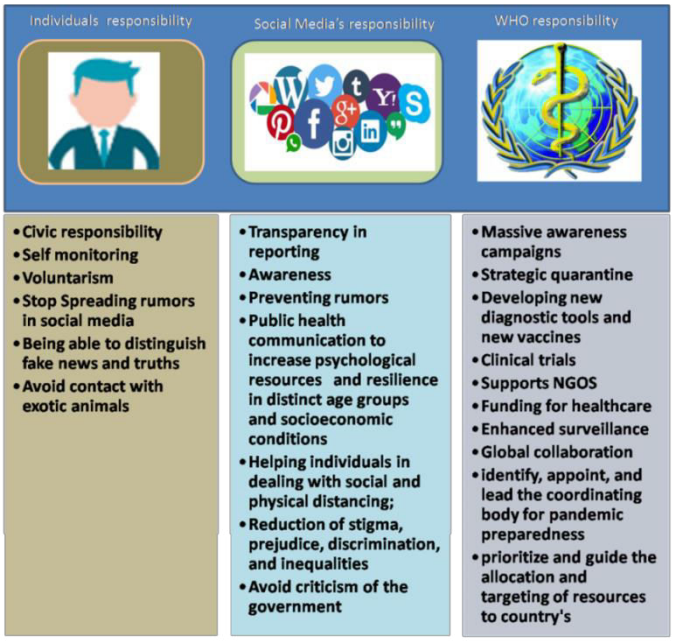

Figure 5: Schematic illustrations of expected responsibilities from the individual, media and government health organizations in containing the spread of 2019-nCoV.

5. Conclusion

With the rapid spread of COVID-19 across the globe, imaging techniques have been a complement diagnostics test for the gold standard RT-PCT and RAD tests. Lung imaging techniques reveal bronchial and pleural modifications. Specifically CT signs of COVID19 include pleural thickening, vascular enlargement and GGO. The combined usage of gold standard and imaging techniques for the diagnosis facilitates rapid tracing of epidemiology. The synergism between artificial intelligence and lung imaging techniques for prognostic prediction of COVID19 becomes primarily important to avoid human errors. However, it is rather prevention than cure by following COVID19 appropriate behavior and cumulative effort of an individual, media houses and government to contain the spread of the virus.

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