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Global Diagnostic Trends of Coronavirus

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Abstract *For the last few months, COVID-19 has had a significant effect on clinical laboratory. This formalized with existing issues and difficulties for the laboratory evaluation of infections owing to extreme acute coronaviral syndrome 2 (SARS-CoV-2). The selection of the relevant respiratory tract specimen from the appropriate anatomical position is key to a timely and correct molecular diagnosis of COVID-19 at the right time in the pre-analytical process. Suitable steps are needed to safeguard laboratory personnel in order to provide accurate test results. The article is aimed at reviewing the literature related to the diagnosis and treatment therapy adapted to compete for novel coronavirus. The study is followed by reviewing 40-45 articles to critically evaluate and extract the possible therapies adapted in the different regions of the world. Serology, radiotherapy, antigen-detection test, point-of-care molecular diagnostics and other radiotherapeutic approaches are found to be efficient and used in several regions of the world.*

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Introduction

Viral infections are responsible for the most commonly occurring infectious diseases and stimulants that lead to significant biological, clinical and socioeconomic problems globally. Meo, S., et al., (2020) Coronavirus (CoVs) belonging to the Coronaviridae family (Nidovirales order) primarily affect the human respiratory system.[Shereen, M.A., et al., (2020), Hamid, S., M.Y. Mir, & G.K. Rohela (2020)] Formerly, coronavirus was believed to be comparatively harmless to humans, but after recent scenarios of extreme acute respiratory syndrome, coronavirus (SARS-CoV) as well as Middle East respiratory syndrome coronavirus (MERS-CoV) outbreaks, which caused serious respiratory infections, took global focus towards CoVs.[Song, Z. et al., (2019)] These coronaviruses have positive-sense single-stranded RNA as their enveloped genetic material. The fact that such zoonotic coronaviruses can be transmitted from an infected animal to other animals when an individual comes into direct contact with the infected animal and from an infected human to others.[Meo, S. et al., 2020]

In December 2019, Wuhan City, Hubei Province, Central China, reported a number of pneumonia cases. The most notable details for many of these cases was their recent visit to a local fish and wild market selling live-ware including poultry, marmots, bats and snakes, exhibiting unknown etiology.[Lu, H., et al., (2020); Li, H., et al., (2019).] Pneumonia of unknown etiology is described as a disease triggered by an unidentified pathogen that meets the following conditions: fever (≥38°C), low or normal white blood cells count or low lymphocyte count, radiographic indications of pneumonia, and no improvement in the symptoms after 3 to 5 days of antimicrobial treatment following standard clinical guidelines.[Li, Q., et al., (2020)] Genome sequencing showed that these pneumonia was triggered by a recently discovered coronavirus which is extreme acuten coronavirus syndrome 2 (SARS-CoV-2), also known as coronavirus 2019 (COVID-19) and which may have been transmitted from bat infecting humans by unidentified intermediate hosts. It was suspected

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that the bat might be the natural host for the virus origin. SARS-CoV-2 is a member of beta coronaviruses, which also includes SARS-CoV and MERS-CoV.[Li, H., et al., (2019), Guo, Y.-R., et al., (2020)]

People of all ages are vulnerable to contract this virus.[Singhal, T., (2020)] Several reports indicated that the most likely cause for the COVID-19 outbreak is a human-to-human transmission. This included direct contact, droplets expelled during cough and sneezing of the infected person. It could also be acquired by touching contaminated surfaces and touching the nose, eyes and mouth afterwards.[Singhal, T., (2020), Rothan (2020)]

The incubation period for the virus, SARS-CoV-2, lies between 2 to 14 days range (5 days mean incubation period).[Linton, N.M., et al., (2020)] The infection caused by the COVID-19 virus can be asymptomatic or symptomatic ranging from mild to severe symptoms.[Surveillances, V., (2020)] Common symptoms comprise of fever, dry cough, muscle pain or tiredness, shortness of breath, whereas symptoms such as headache, diarrhoea, sputum production, losing the sense of taste and smell, discolouration of fingers or toes, or rash on the skin, were not uncommon.[Huang, C., et al., (2020); WHO 2020]

Factually there has been no specific antiviral drug or any type of vaccine available for the treating COVID-19 infection to date.[Rothan, H.A. (2020)] So far, antivirals are used as main treatment, which interfere with the virus ability to enter cells and preventing multiplication of the virus. Clinical management involves prevention from infection, control measures to minimize the occurrence of the disease and certain supportive treatments which include supplementary oxygen and mechanical ventilation when necessitated.[Abd El-Aziz., et al., 2020] The Centers for Disease Control (CDC) and World Health Organization (WHO) have issued recommendations to prevent further spread of the illness by maintaining social distance, regular hand washing and avoiding crowded places.[Centers for Disease Control and Prevention 2020 , World Health Organization 2020b]

Methodology

Extensive literature is readily available regarding the pandemic COVID-19 disease. For writing this review article, authors have reviewed approximately 40-50 articles. This review article highlights the information associated with diagnosis and treatment therapy adopted for novel coronavirus to date.

Global Diagnostic Trends of Covid-19

As indicated by the World Health Association, the crown infection is spread to Worldwide and affected very nearly 2544792 individuals on the planet and cause 175694 passing till 23 April 2020.[WHO (2020)c] This virus can be transmitted to humans and has evidence of human to human transfer. Another possible course of transmission, fecal-oral transmission, has not yet been verified.[Li, Y. (2019), Dai, W.-c., et al., (2020)] On January 30, 2020, a worldwide health emergency has been declared by WHO against the episode of COVID-19[Li, Y. (2019)]. A few instances of COVID-19 were recorded in 24 separate countries from February 19, 2020, including Thailand, Australia and the USA. This scene demonstrates the need for fast and effective detection and recognition strategies that can be used for determination of COVID-19 and the patient board in neighbouring clinics and facilities.[Li, Y. (2019), Ai, T., et al., (2020)]

As there is no proper treatment or vaccinations for the 2019 novel coronavirus d isease (COVID-19), it is very essential to diagnose the viruses at an early stage and isolating the aff ected individual from the safe Community immediately is important. Increasing the ability for testing would enable physicians to consider COVID19 t reatment in some cases with a larger community of symptomatic patients and people without sy mptoms.[Chan, J.F.-W., et al., (2020]

Here we will discuss the globally diagnostic techniques of coronavirus disease (COVID-19); we will target some specific countries where this virus shows a greater disaster.

Diagnostic Techniques of Coronavirus Disease in China

The aggressive pneumonia outbreak, named SARS-CoV2, was associated with a novel coronavirus in the province of Wuhan, Hubei, China.

As of December 2019. In the subsequent weeks, diseases spread across China and other countri es across the world [Azhar, E.I., et al., (2020)]. The disease is ended by a group of international experts with a number of backgrounds

collaborating with Chinese peers.[Giovanetti, M. et al., (2020)]

Computed tomography (CT) interpretation is required for the auxiliary diagnosis in the initial screening. 3 The diagnosis is then confirmed by positive outcomes of the Nucleic Acid Enhancement (NAAT) or Blood Specimens Reverse Real-Time Polymerase Chain Reaction (RTR) analysis (RT-PCR). Nevertheless, this methodology of the study is highly limited. If the viral burden is strong, the identification rate is low, which contributes to false findings. There can be only a positive decision, but the seriousness and the development of COVID-19 cannot be determined (CT imagery can, of course, uncover disease progression) [Li, Y. & L. Xia, (2019)].

Although a Real-time RT-PCR assay was successfully manufactured and used as a guide standard in the correct diagnosis of COVID-19 infection, its high rate of false-negative outcomes and its inaccuracy during the initial phase of outbreak limited the diagnosis of people with the COVID-19 virus. [Chan, J.F.-W., et al., (2020)] Radiological examinations plays an important role during the diagnosis of this infectious disease. [Wang, S.-x., et al., (2020)] Chiefly thin slice chest Computed Tomography (CT) can be used for the detection of early-phase lung infection to facilitate timely response against the infection. [Chan, J.F.-W., et al., (2020)] At present, in Hubei, The results of China chest CT were proposed as significant proof to support the diagnosis of the infection. [Wang, S.-x., et al., (2020), Chan, J.F.-W., et al., (2020)]

Complete Blood Count and other Methods

Initial investigations for the detection of the virus include performing a complete blood count (CBC), coagulation profile as well as analyzing serum biochemical tests result which includes renal and liver function, creatinine kinase, lactate dehydrogenase, and electrolytes. China Food and Drug Administration (FDA) approved the use of RT-PCR assay for the detection of respiratory specimens including common viruses such as influenza, adenovirus, respiratory syncytial virus, adenovirus, para-influenza virus, SARS-CoV, and MERS-CoV obtained through nasal and pharyngeal swabs, Broncho-alveolar lavage fluid, sputum, or bronchial aspirates. Scheduled bacterial and fungal checks were also executed. [Huang, C., et al., (2020)]

The Role of Radiology in Detection of COVID-19 Infection

For the early detection and management of COVID-19 infection, radiological examinations have great significance. Chest radiography may exhibit normal findings during the initial stage of the infection, as during detection of ground-glass opacity (GGO) it shows no sensitivity. [Huang, C. et al., (2020)] The suspected COVID-19 patient should be immediately quarantined even if the patient's Nucleic Acid Amplification Test (NAAT) result is negative but shows positive imaging result and should be treated on priority. [Dai, W.-c., et al., (2020)] The contribution of the radiological test to the proper diagnosis of the infection is very obvious. The original lung findings from chest CT indicate that tiny subpleural GGOs have developed bigger with an insane paving trend and have risen over two weeks after the initiation of a disease. After two weeks, the lesions were gradually absorbed, leaving large GGOs and subpleural bands behind them. [Dai, W.-c., et al., (2020), Chan, J.F.-W., et al., (2020)]

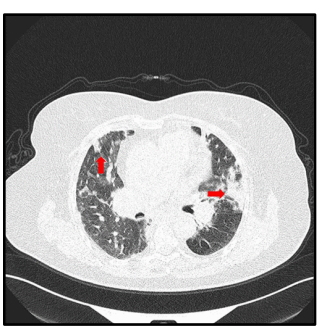

Figure 1: High-resolution chest CT scan of a 60 year old female showing widespread patchy exudates along with the consolidation of both lungs, vague GGOs were also seen on edge, in addition to interlobular septal thickening shown by red arrows. [Dai, W.-c., et al., (2020)]

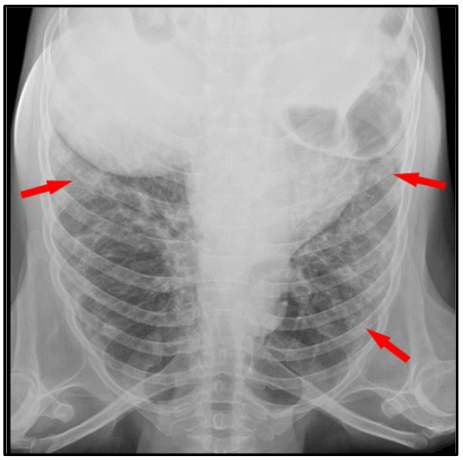

Figure 2: Chest radiography shows multifocal patchy opacities in both lungs indicated by red arrows in a 53-year-old confirmed COVID-19 female patient who had fever and cough for five days. (Surveillances, V., (2020))

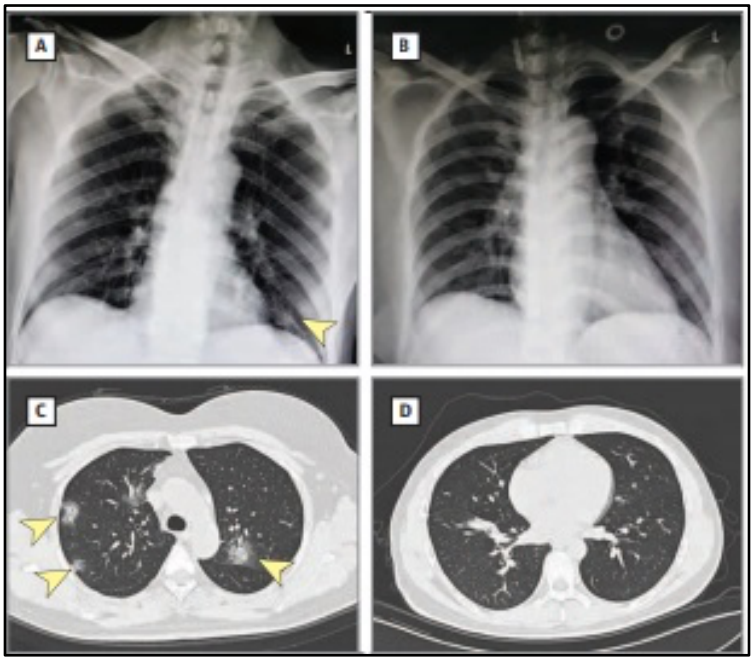

Figure 3: (A) Scattered opacities in lower left lobe in chest radiograph from a 69-year-old man shown by the arrowhead. (B) 32-year-old women normal chest radiograph. (C) Chest CT scan shows bilateral GGOs in a 49 year old women pointed out by arrowheads. (D) 34-year-old normal chest CT scan.

CT Imaging Finding

The chest CT scan of COVID-19 patients shows common evidence of GGO, consolidation, crazy-paving pattern, and reticular pattern. Atypical manifestations seen in CT scan includes pleural changes, airway changes, fibrosis and nodules etc.[Ye, Z. et al., (2020)]CT scan obtained during the first week of infection shows in the lower area of the lungs, more extensive GGO

(multifocal, peripheral, pure GGO, and mixed GGO) than consolidation with slight predominance. [Cheng, Z., et al., (2020)]

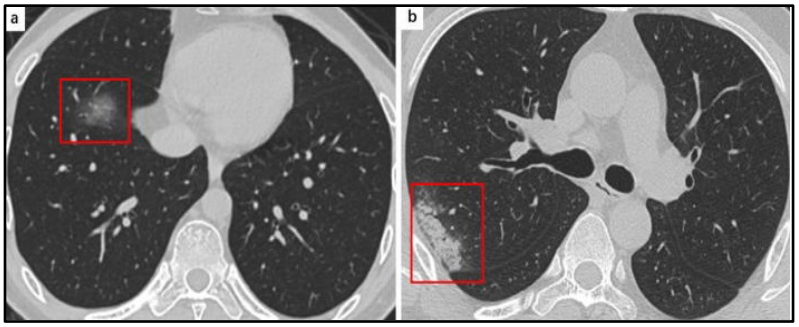

Figure 4: (a) In the right lower lobe of a 35-year-old confirmed COVID-19 male patient with symptoms of fever and headache for the past one day, pure GGO can be identified from a CT scan displayed with red border. (b) In the red frame, consolidation in the right lobe sub-pleural region of a 47-year-old COVID-19 patient with symptoms fever for 7days is seen using CT scan.

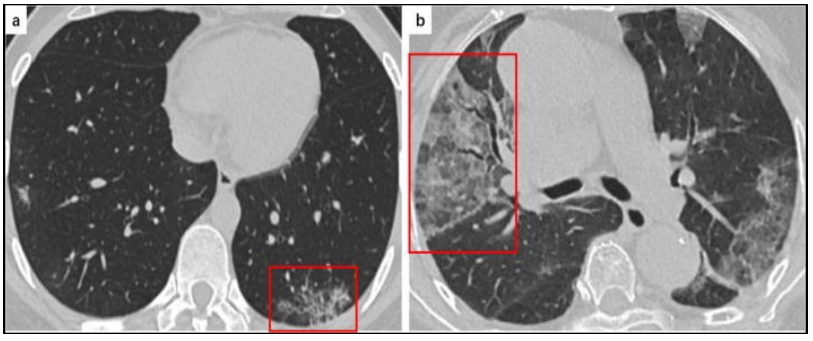

Figure 5: (a) Slight reticular pattern seen in CT scan of a 34-year-old confirmed COVID-19 female patients with symptoms fever and dry cough for two days in the lower left lobe and sub-pleural area highlighted in red frame. (b) CT scan of a confirmed case of COVID-19 81-year-old female patient with fever and cough for 7 days shows GGO superimposed with reticular pattern which resembles the sign of crazy-paving stone indicated in red frame in the right middle lobe.

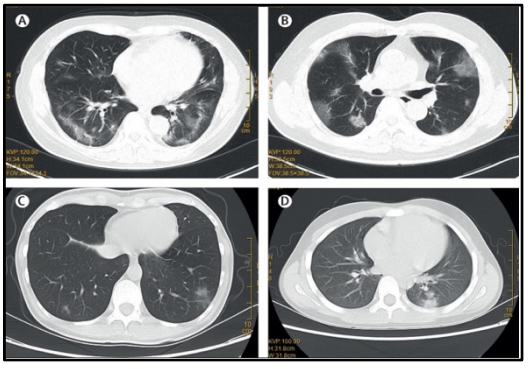

Figure 6: Thoracic CT scan of 4 different patients shows multifocal ground-glass changes in lungs.

A research consisting of 21 confirmed COVID-19 patients took place in China regarding the lungs morphological changes seen in chest CT scan of these patients indicates, involvement of more

than 2 lobes in 15 (71%) of the patients, GGO seen in 12 (57%) patients, opacities with rounded morphology observed in 7 (33%) patients, consolidation along with GGO in 6 (29%) patients, crazy-paving patterns is seen in 4 (19%) patients, 3 (14%) patients presented with normal CT scan. Pleural effusions, lung cavitation, pulmonary nodules, lymphadenopathy were absent

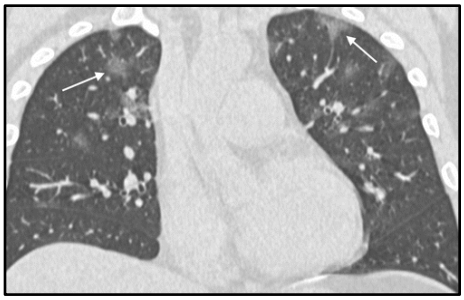

Figure 7: CT image of a 36-year-old male patient having recent travel history to Wuhan with symptoms fever, fatigue, and myalgia shows GGO with rounded morphology in both upper lobes of the lungs.

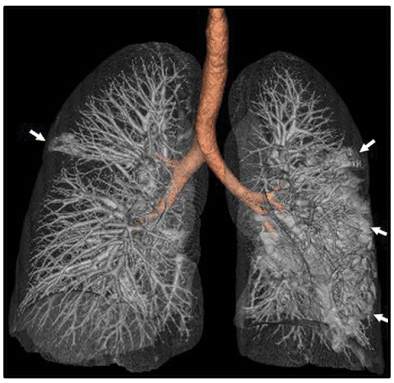

Figure 8: Chest CT scan were performed showing ground-glass opacities and lingular segment in right upper lobe and left lower lobe respectively, after sputum real-fluorescence polymerase chain reaction assay conducted for 2019 novel coronavirus shows negative result for a 36 year old man who had developed fever, sore throat, and fatigue after travelling to Wuhan, China.

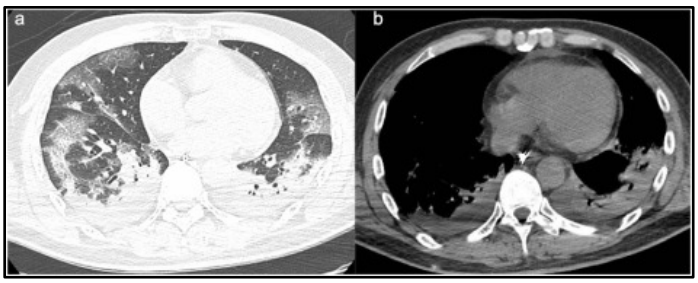

Figure 9: An Axial CT scan done 10 days after the onset of symptoms of a 42-year-old male patient shows bilateral consolidative opacities, with rounded morphology in left lower lobe, and with striking peripheral distribution in right lower lobe.

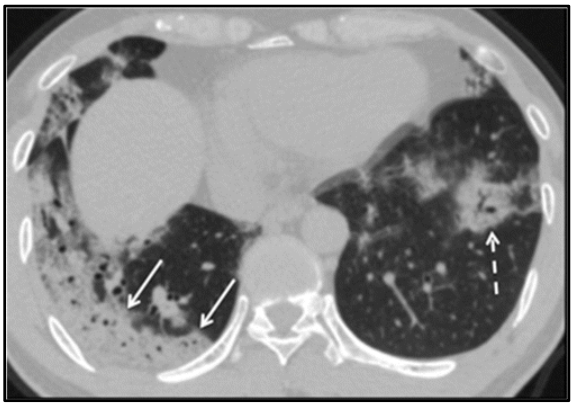

Figure 10: Gradual degradation of lung parenchyma seen via baseline CT and follow-up CT displayed through lung VCAR imaging. Lung sparing analysis.[36]

Diagnostic Techniques of Coronavirus Disease in Italy and Spain

The latest coronavirus epidemic for 2019 was first identified in Italy, when a pair travelling from Wuhan, China, were admitted to Italy on 29 January 2020 at the Lazzaro Spallanzani National Institute of Infectious Diseases, Rome with respiratory tract and fever symptoms. [Albarello, F., et al., (2020)] Next month on February 20, 2020, in Lombardy region of Italy a man with atypical pneumonia was admitted which later confirmed as COVID-19. In the following 24 hours, 36 new cases emerged having no known contact with the first patient or anyone known to have COVID-19.[Livingston 2020] Laboratory test results for respiratory samples confirmed SARS-CoV2 infection. Some notable imaging test results were observed of the first couple confirmed with COVID-19 infection travelling from Wuhan, China. Progressive Adult Respiratory Distress Syndrome (ARDS) was in in chest X-Rays and CT scans. [Albarello, F., et al., (2020)]

Imaging Findings: Chest X-Ray and CT Scan

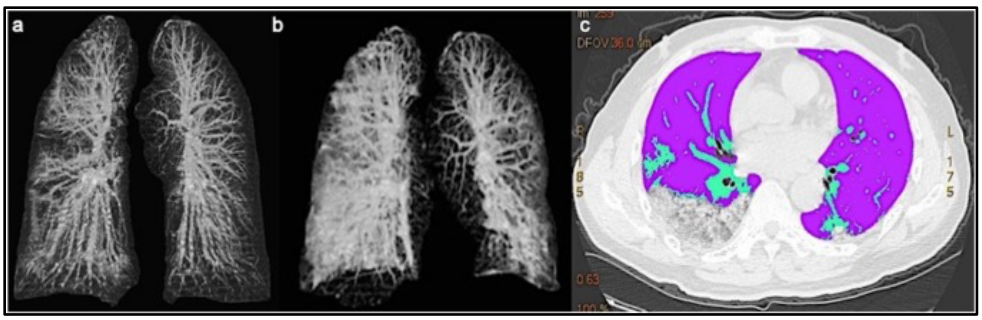

Figure 11: (a) Severe progression of pneumonia with increase extension of GGO and consolidation seen via follow-up CT of a 66-year-old man after 5 days. (b) Bilateral pleural effusion manifestation seen. (Overview of Testing for SARS-CoV-2)

Chest CT scan and X-ray are assessed for the confirmation of novel coronavirus 2019 infection. While evaluating chest X-ray presence of interstitial involvement either reticular, nodular or mixed pattern, presence of pleural effusion, lung opacities, hilar enlargement, cardiac silhouette, mediastinal lines indicates SARS-CoV-2 infection. [Albarello, F., et al., (2020)]

Laboratory Testing

126 samples of nasopharyngeal swab specimens were collected from different hospitals and were referred to INMI Laboratory of Virology (54 specimens from high isolation facility at INMI in Rome, 9 from hospitals in Lazio region, 63 from different regions of Italy). [Bordi, L., et al., (2020), Escalera-Antezana, J.P., et al., (2020)]Real-time reverse transcriptase PCR were performed for nasal swabs and were analyzed by molecular virology unit of the hospital following WHO guidelines and Corman et al protocol, confirming positive SARS-CoV-2 infection.[Escalera-Antezana, J.P., et al., (2020), Colaneri, M., et al., (2020)]

Body Temperature and Symptoms

According to COVID-19 Diagnosis and Treatment Protocol Trial Version 7, body temperature should be considered one of the key symptom while assessing COVID-19 infection i.e. evaluated for more than three days after returning to normal. In addition to body temperature noticeable improvement of respiratory symptoms, and obvious reduction in inflammation should be seen in pulmonary imaging. To properly assess the treatment efficacy towards COVID-19 infection, the lung imaging of the infected patients should be carefully evaluated, as per the description of lung segment and density criteria (high, medium and low grades).[Wang, S.-x., et al., (2020)]

Diagnostic Techniques of Coronavirus Disease in United States

The Secretary of Health and Human Services (HHS), on February 4th, 2020 recognized the spread of infection caused by SARS-CoV-2 as global emergency where in the utilization of in-vitro testing for proper diagnosis and detection of the infection was justified. The availability of diagnostic testing was imperative for rapid detection of COVID-19 patients to limit the spread of the infection. However, RT-PCR based assay on respiratory specimens performed are the base for the COVID-19 diagnosis, but this guidance promoted the laboratories and manufacturers to accelerate the manufacturing of other tests as well for more rapid testing of infection in the United States.[FDA (2020) ; Corman, V.M., et al., (2020)]

Laboratory-Based Molecular Testing

On February 29th, 2020, utilization of laboratory-developed tests for SARS-CoV-2 detection were allowed by the FDA without taking into account prior agency approval. (30) Although oro-pharyngeal, mid-turbinate, anterior nares specimens are also acceptable for SARS-CoV-2 testing, but nasopharyngeal sample testing is preferred. (31) To improve the collection and release of cellular material, samples must be taken using a flocked swab. Ideally swabs with shafts made of aluminum and plastic are preferred. Swabs that may contains certain substances that may inhibit PCR testing such as calcium alginate, cotton, or wood should be avoided. [Cheng, M.P., et al., (2020)]

On 9 March 2020, a 31-week-old 41-year-old woman, with hypothyroidism and gestational hypertension, was admitted to Hospital Escuela in Tegucigalpa, Honduras with a three-day complaint of irregular fever, headache, dry toxins and myalgia. She's travelled back to Madrid, Spain, where she has been residing for the last six months. Your Madrid, Spain neighbours were afflicted with COVID-19. Provided their travel background and symptoms, nasopharyngeal specimens were taken and checked in compliance with the WHO Protocols for the RT-PCR at the National Virology Laboratory in Tegucigalpa under the Charité, Berlin, Germany Procedure. The findings were good and the patient was isolated in the hospital. [Zambrano, L.I., et al. (2020)]

Point-of-Care Molecular Diagnostics

Rapid test results within one hour and low-complexity molecular diagnostic tests for viral infections of the respiratory system that are CLIA waived (approved by the FDA to be used outside the laboratory by non-laboratory personnel) includes cartridge-based assays on platforms comprising the Abbott ID NOW (Abbott Laboratories), Cobas Liat (Roche Diagnostics), BioFire FilmeArray (bioMérieux), and GeneXpert (Cepheid). Such instruments will be critical to

expand point-of-care testing for SARS-CoV-2 rapid point-of-care assays. The GeneXpert (Cepheid) platform had received EUA (Emergency Use Authorization) by the FDA for Xpert Xpress SARS-COV-2 test, which is extensively used particularly in low- and middle-income countries for HIV and tuberculosis testing. This capacity might be helpful to broaden testing worldwide and it would enable clinical decisions in settings where rapid results at the point-of-care is needed, though testing throughput might be a limiting factor.[Corman, V.M., et al., (2020), Cheng, M.P., et al., (2020)]

Antigen Detection Tests

Tests utilizing immunoassay procedures for the detection of influenza virus or syncytial virus antigens directly from the clinical specimens have been commercially available decades-long. These tests are of low complexity and the results are obtained within minutes. (Huang, P., et al., (2020)) Current tools for respiratory syncytial virus and influenza virus are not of highest standard to eliminate the disease, and the same question would arise for SARS-CoV-2, therefore clear guidance regarding the correct interpretation should be implemented for the tests. (33, 35) Prototypes for such tests for coronaviruses are still under development and have not obtained regulatory approval. Monoclonal antibodies have been generated against the nucleo-capsid protein of SARS-CoV-2, which might be beneficial for rapid antigen detection test in the near future.[Cheng, M.P., et al., (2020)]

Serology

Serologic tests such as Enzyme-Linked Immunosorbent Assays (ELISA) are performed on clinical specimens for instance saliva or blood for the identification of antibodies (IgA, IgM, and IgG) against SARS-CoV-2 and is capable to be employed for diagnosis in certain circumstances. [Cheng, M.P., et al., (2020)]

Radiographic Tests

For diagnosis many centers have evaluated the utilization of chest imaging. On chest radiography, the most frequent feature observed is bilateral pneumonia (11.8%-100%) as compared to unilateral focus. [Cheng, M.P., et al., (2020), Organization, W.H., (2020)]

The competence of awareness, flexible isolation systems and intensive case findings were demonstrated by some of the Asian Countries. South Korea significantly slowed the spread of the infection by performing extraordinary number of tests every day. (Li, Y. & L. Xia, (2019)) More than 300,000 tests i.e., 5828.6 tests per million people were performed in South Korea within 9 weeks after the detection of first COVID-19 case. (Li, Y. & L. Xia, (2019), Dai, W.-c., et al., (2020)) Singapore followed aggressive contact tracing, broad case definition, and isolating the infected patients, on top of that Singapore also screened patients with pneumonia, influenza-like illnesses present in hospital settings, primary-care settings, intensive care for severely ill patients to detect possible infected person.Similar tactics were followed by Taiwan and Hong Kong. (Ai, T., et al., (2020)) Resource-intensive approaches prioritizing aggressive testing and isolation were implemented for rapid interruption of transmission from infected people. (Li, Y. & L. Xia, (2019) Dai, W.-c., et al., (2020))

Conclusions

Globally, the current, unparalleled epidemic of COVID-19 has highlighted how important diagnostic detection of human coronavirus infections is to reduce the spread and properly manage patients with severe infections. This comment has discussed existing concerns relevant to SARS-CoV-2 research. The study has successfully brought insights into the diagnostics and treatment approaches of coronavirus being used in the different countries. The authors in this study were more interested in evaluating the treatment especially in US, Italy and Spain. The literature has proven that laboratory testing, body temperature and general symptoms for COVID-19 are some of the basic approaches used in all over the world. More specifically chest X-Rays and CT-Scans, serology, Antigen-detection diagnosis and point-of-care- molecular diagnosis are seen to be used in the most critical diagnosis.

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