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Review Article

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The global COVID-19 pandemic

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Abstract

The Chinese government at the end of 2019, informed the World Health Organization (WHO) that many cases of uncommon etiology pneumonia have been investigated in the Hunan seafood market and infected more than fifty persons. This seafood market sold snakes, bats, frogs, birds, marmots, and many other animals. On 12 January 2020, the National Health Commission of China released information concerning this outbreak, proposed that the causative agent of pneumonia is viral. However, depending on the genetic sequence and the sequence-based analysis of specimens of the infected patients, the diagnosed virus was named Coronavirus. WHO officially stated on 30 January 2020, that the coronavirus disease (COVID-19) outbreak as an international health emergency was rapidly extended throughout China. Europe has also become a new epicenter of COVID-19. These cases have been spread across the world with the worst situations reported in Italy. As per the WHO report on March 17, 2020, the cases outside China have exceeded. However, investigations revealed that this viral disease could be transmitted from human to human. Meanwhile the common symptoms of this viral disease involved, sore throat, fever, fatigue, cough with shortness of breathing. The greatest cases showed mild symptoms, while other cases exhibit progress to pneumonia and multi-organ failure particularly in patients suffering from underlying diseases and the elderly.

Keywords Acute Respiratory Disease, Pneumonia, Coronavirus Infection, Viral Diseases, Pandemic Diseases.

Introduction

Both animals and the environment have considerable relationships for the occurrence of emerging zoonotic diseases in animals and humans (Bonilla, Suarez, Franco, and Vilcarromero 2019). There is a wide range of infectious diseases within zoonotic diseases, caused by parasitic, fungal, viral, and bacterial. In particular, emerging diseases are usually associated with animal and environmental factors, (Ellwanger and Chies 2018). However, over the past two decades, the devastating capability of coronaviruses is continuously evolving, resulting in fatal outbreaks that reveal a considerable threat to global public health (Munster, Koopmans, and van Doremalen 2020). The coronavirus disease emerged in the Hunan seafood market in Wuhan city of China (Liu and Saif 2020), causing respiratory manifestations in infected patients. This RNA virus is transmitted via drops and airborne particles (Rodriguez-Morales, MacGregor and Kanagarajah 2020). The

first analysis of cases proposed a common exposure point for all of the infected patients, the seafood market in Wuhan city (Hui et al., 2020). This market sells bats, poultry, snakes, and marmots. Such a wet- place is hotspots represent human-animal interphase. It is an ideal place where novel zoonotic viruses could jump the species barrier causes the emergence of novel pathogens (Malik et al., 2020). On 7th January 2020, the Chinese scientists rapidly isolated the coronavirus from a patient and submitted the specimen to genome sequencing. On 11 February 2020, (WHO) officially identify this disease as coronavirus disease 2019, and on 12 January 2020 WHO named this coronavirus, as the 2019- novel coronavirus (2019-nCoV) (Lu et al., 2020), and found out that the coronavirus single-stranded RNA beta-corona virus with highly identical genome to bat coronavirus, with the consideration that bat as the natural host (Yan-Rong et al., 2020) (Figure 1). But other mammals could be involved as intermediate hosts (Malik et al., 2020). The tiny size coronaviruses (CoVs) comprise a nucleic

material represented by a single-stranded RNA (Zhong et al., 2003). However, Coronaviruses belong to the family Coronaviridae, RNA viruses that cause infectious diseases in human beings (Lim, Ng, Tam and Liu 2016; Weiss and Leibowitz, 2011). This family comprises 4 types: Alpha, Beta, Delta, and Gamma coronavirus. Two coronaviruses cause a clinical significant in infecting humans; the genus Beta coronavirus results in severe acute respiratory syndrome (SARS-CoV) from B-lineage and the Middle East respiratory syndrome (MERS-CoV) from C lineage (Kuiken et al., 2003). Recently, the third coronavirus strain from B lineage, the (SARS-CoV-2), the cause of coronavirus disease (COVID-19) that arise in seafood market in Wuhan city, at end of 2019 (European Centre for Disease Prevention and Control [ECDC], 2020). On the outer surface of the coronavirus there are crown-like spikes (thus, it was called a coronavirus). The coronavirus utilizes the receptor, angiotensin-converting enzyme 2 (ACE2) the similar receptor as that for SARS-CoV, and mostly infected the respiratory tract (Yan-Rong et al., 2020). Several European countries were suffered a local transmitted and increasingly spread of this viral disease of coronavirus disease (Lim et al., 2016).



Fig 1. Illustrate SARS-CoV-2 and horseshoe bats, the most natural reservoirs (Yuefei et al., 2020).

Genome structure

Coronaviruses included many changeable additional genes that were placed in two clusters in the 30-terminal one-third of the genome. The genes vary obviously regarding their specific nature and genomic position among the coronavirus categories, with specific for each category. These refer to (group-specific genes) (Shen, Wen, and Liu, 2003). Human Beta coronavirus for (SARS-CoV, MERS-CoV, and SARS-CoV-2) genome involved the 5'-untranslated region (5'-UTR), open reading frame (ORFs), accessory proteins, structural proteins, and the 3'-untranslated region (3'-UTR) (Figure 2). Recently it has been investigated that there are notable differences between SARS-CoV and SARS-CoV-2 like the absence of 8a protein and variation in the number of amino acids in 8b and 3c protein in SARSCoV- 2 (Adnan, Khan, Kazmi, Bashir, and Siddique, 2020) (Figure 3). Additionally, the coronavirus genome is composed of structural proteins as well as different numbers of (ORFs) (Song et al., 2019). Most of the viral RNA is located in the first ORF (ORF1a/b) which translates (pp1a and pp1ab) a polyprotein and encodes sixteen non-structural proteins (NSP). The rest of ORFs encode accessories like ORF 3, 6, 7a, 7b, 8, and 9b in the SARS-CoV-2 genome (Cui, Li, and Shi, 2019).

However, the specific genes in ORF1 downstream regions encode proteins for viral replication, spikes formation, and nucleocapsid (van Boheemen et al., 2012). The structural proteins are encoded by the 4 essential structural genes, involving spike (S) glycoprotein, envelope (E), membrane (M), and nucleocapsid (N) genes (Cui et al., 2019) (Fig. 4). The glycoprotein spikes on the outer surface of coronaviruses are responsible for virus-cell receptor interactions during viral entry to host cells (Zumla et al., 2016). In terms of the genomic and phylogenetic similarity to SARS-CoV especially in the receptor-binding domain (RBD) and S-glycoprotein gene, the genome of the SARS-CoV-2 investigated to be 80% identical to the (SARS-CoV) which propose the capability of direct transmission of COVID-19 to human. Moreover, most of the SARS-CoV-2 genomic encoded proteins seem to be the same as those of SARS-CoVs, although the involved variance. Wuet al., (2020) cited that “At the protein level, there are no amino acid substitutions exist in NSP7, NSP13, envelope, matrix, or accessory proteins p6 and 8b, except in NSP2, NSP3, spike protein, underpinning subdomain like RBD. SARS-CoV-2 is closer to the SARS-like bat CoVs regarding the whole genome sequence”.

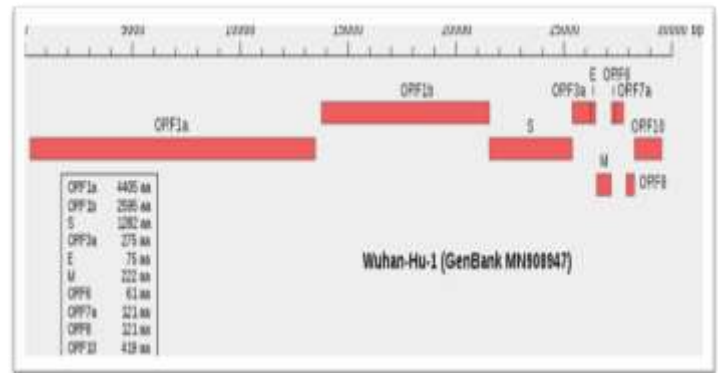


Fig 2. Genomic organisation of SARS-CoV-2 (Wuhan-Hu-1, GenBank AccMN908947).



Fig 3. Betacoronaviruses genome organization (Adnan et al., 2020).

However, Zumla et al. (2016) reported "that “SARS-CoV-2 genome encodes structural proteins as spike glycoprotein and accessory proteins. The SARS-CoV-2 genome also encodes non-structural proteins (NSP) such as 3-chymotrypsin-like protease, RNA-dependent RNA polymerase, helicase in addition to papain-like protease, while the four non-structural proteins are key enzymes in the viral life cycle”. Morse, Lalonde, Shiqing, and Liu (2020) also cited that “the Initial

analyses of genomic sequences from SARS-CoV-2 indicate that the catalytic sites of the four SARS-CoV-2 enzymes are highly conserved and have a high level of sequence similarity with the corresponding SARS and MERS enzymes”.

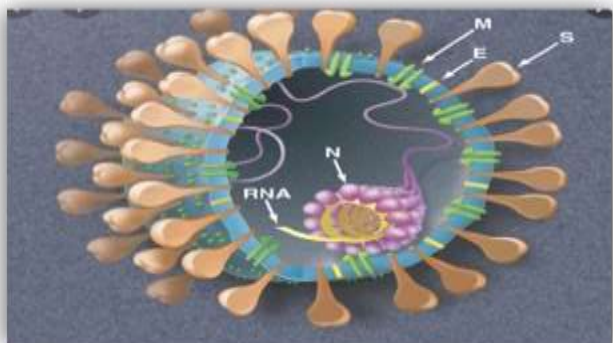


Fig 4: Illustrate the structure of human coronavirus. Spike (S), envelop (E), membrane (M) and nucleocapsid (N) proteins are the structural proteins [www.google.com].

During viral entry, the spike glycoprotein is necessary for interactions between the virus and cell receptor (Zumla et al., 2016). Glowacka et al. (2011) explained the entry mechanism of a coronavirus and cited “it relies upon cellular proteases including human airway trypsin-like protease (HAT), transmembrane protease serine 2 (TMPRSS2) and cathepsins that split the spike protein and establish further penetration changes”. In fact TMPRSS2 activates the SARS coronavirus spike protein for membrane fusion and decreases viral control by the humoral immune response. It was improved in a fluorescent study, that the SARS-CoV-2 also utilizes the same host cell receptor, the angiotensin-converting enzyme 2 (ACE2), and enters to host cell by the same mechanism used by the SARS-CoV (Xu et al., 2020). Li et al. (2020) also cited that “spike glycoprotein of the Wuhan coronavirus has been modified via homologous recombination. In fact SARS-CoV-2 spike glycoprotein is a mixture of bat SARS-CoV and a not known Beta-CoV” in SARS-CoV-2’s spike protein, the single N501T mutation may have remarkably enhanced its binding affinity for the host cell receptor (ACE2) (Wan, Shang, Graham, Baric and Li, 2020). Furthermore, Zhang, Shen, Chen, and Lin (2020), analyzed the genotypes of COVID-19 in patients from districts and territories and revealed that SARS-CoV-2 had been mutated in many patients in China.

The life cycle of SARS-CoV-2

The hallmark of coronaviruses under the electron microscope is the S protein which comprises the spikes. de Groot et al., (1987) and Cavanagh (1995) cited that “it is a relatively large, (1160 to 1452 amino acid-long type I glycoprotein) with a cleavable N-terminal signal sequence and a membrane-anchoring sequence followed by a short hydrophilic carboxy-terminal tail of about 30 residues. It is the main determinant of host range, pathogenesis, and virulence. However, all coronaviruses encode spike of the virion, a surface glycoprotein (Li, 2016), which binds to receptor ACE2, on the human cell

surface (Tortorici and Veesler 2019), and mediates viral entry (Li, 2016).

A receptor ACE2 represents a major part of the humans lower respiratory tract (Jia et al., 2005) and regulates human-to-human transmission (Wan et al., 2020). Zhou et al., (2020) improved that the SARS-CoV-2 utilizes ACE2 which is the same cellular entry receptor, as SARS-CoV. However, spike glycoprotein also called the receptor-binding domain (RBD) (Simmons, Zmora, Gierer, Heurich and Pohlmann 2013), is a single, continuous domain (Michael, Andrea and Vincent 2020), that has all of the information essential to interact with the human receptor. A single, continuous domain has the potential of folding independent of the rest of the spike glycoprotein (Li F, Li W, Farzan and Harrison 2005).

Meanwhile, coronavirus entering into host cell comprises several domains in a spike that mediate virus attachment to the host cell surface. Entering coronavirus into the host cell is a multi-step process (Li, 2016). After virus entry and binding the host receptor, an adjacent host protease cleaves the spike, which releasing the spike fusion peptide, and facilitates virus entry (Matsuyama et al. 2010). Glowacka et al. (2011) reported that the mechanism of a coronavirus entry into a human cell relies on host proteases that contain cathepsins, trypsin-like protease (HAT), and transmembrane protease serine 2 (TMPRSS2) that capable to split the spike glycoprotein and organize more penetration changes. Recent studies have focused on the essential role of the cellular protease activities which are considered as a specific species barrier (Beniac, de Varennes, Andonov, He and Booth 2007). Some studies have been investigated that human proteases that have the ability to cleave the spike, allowing for downstream membrane fusion, while some studies proposed that protease may activate the receptor (Shulla et al., 2011). Furthermore, a study done by Becker et al. 2008 investigated that substitute the RBD of the lineage B bat virus Rp3 could permit the expressing human ACE2 after the virus entry to the host cells (Becker et al., 2008). Based on the Cryo-EM structure analysis of S proteins, SARS-CoV-2 spike glycoprotein had (10 - 20) fold greater attraction to human ACE2 receptor than that of SARS-CoV (Wrapp et al., 2020). ACE2, investigated in the humans’ lower respiratory tract (Jia et al., 2005), presents in massiveness on epithelial cells of lung alveolar as well as in the small intestine enterocytes (Hamming et al., 2004). The mechanism of virus entry is represented by the binding of SARS-CoV-2 spike glycoprotein and ACE2 host receptor as a critical step for virus attachments and penetration (Letko, Marzi, and Munster 2020). The change in the spike protein after receptor binding assists and make it possible for viral envelope fusion with the human cell membrane via the endosomal pathway. After membrane fusion, viral genome RNA is released into the host cell cytoplasm. The uncoated RNA translates two polyproteins (pp1a and pp1ab) (de Wilde, Snijder, Kikkert, and van Hemert 2018). By viral proteinases, these two polyproteins cleaved into tiny products, and by discontinuous transcription, the polymerase produces which is a series of subgenomic mRNAs eventually translated into pertinent viral proteins (Adnan et al., 2020). As cited by Laude and Masters (1995) “the ribonucleoprotein (RNP) core consists of one copy of the viral genomic RNA which is then packaged into a helical structure in the cytoplasm of the host cell by multiple copies of

nucleocapsid protein (N). Meanwhile, the (S, M and E), structural proteins are inserted into the rough endoplasmic reticulum (RER) membrane, transfer to the endoplasmic reticulum (ER) then to Golgi intermediate compartment (ERGIC) to join the nucleocapsid, and by budding arise into particles. However, in this process, the M protein has a critical role via reacting with all viral assembly partners. It forms a

basic matrix of the viral envelope. M molecules react with the E and S envelope proteins in addition to nucleocapsid, thereby manage and direct the structure of the virion (Cornelis and Peter 2005). Eventually, the virion involving vesicles fused with the host cell plasma membrane to release the virus out of the host cell (Adnan et al., 2020) (Fig. 5).

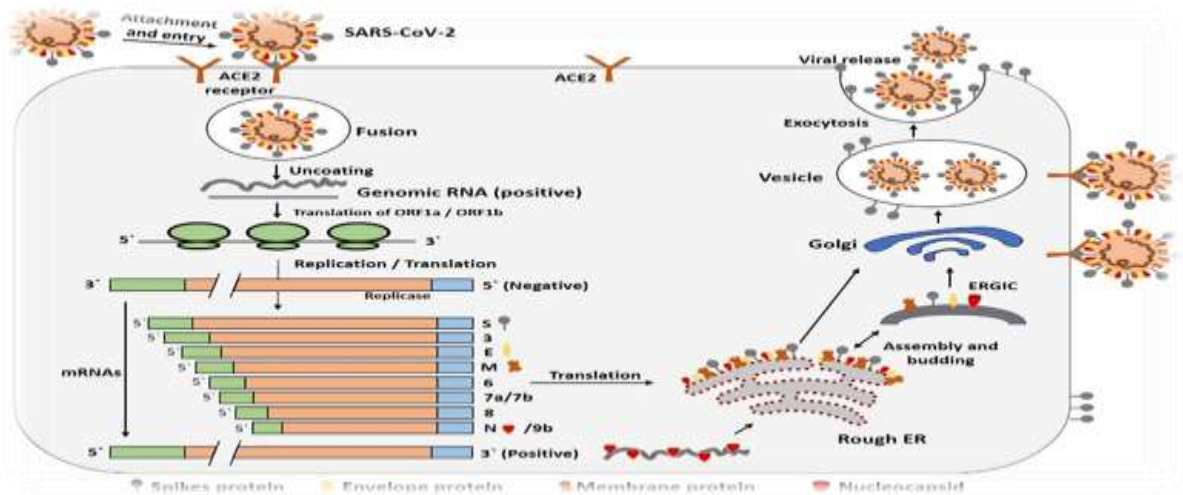


Fig 5. Illustrate the life cycle of coronavirus. ER, endoplasmic reticulum; ERGIC, ER- Golgi intermediate compartment (Adnan et al., 2020).

Signs and symptoms

Clinical registration investigated that there are asymptomatic patients diagnosed with SARS-CoV-2 (Bai et al., 2020; Chang et al., 2020), depending on positive viral nucleic acid test results, without any symptoms of COVID-19, like fever, respiratory, or gastrointestinal symptoms (Liu, Liao, Chang, Chou and Lin 2020; Rothe et al., 2020). They develop fatigue, fever, cough, and shortness of breath (Huang et al., 2020), but on a chest radiograph, there aren't significant abnormalities. Asymptomatic carriers could transmission COVID-19 via person-to-person contact (Liuet et al.,2020; Rothe et al., 2020) and can spread the virus and may easily neglect in epidemic prevention (Bai et al., 2020). Thus it is so necessary to differentiate asymptomatic patients infected with COVID-19 (Laiet et al., 2020). However, the incubation period for COVID-19 is lasted from5-6 days but may range from 2-14 days (Laueret et al., 2020; Centers for Disease Control and Prevention [CDC] 2020). It is important to record the time between the infection with COVID-19and the appearance of symptoms, for infection control for the duration of isolation (Li et al., 2020). However, Guan et al., (2020)proposed that the median incubation period was only three days, but may last to twenty-four days. While Wang et al.,(2020) observed that the median time from symptom manifestation to acute respiratory disease was about eight days. Although the COVID-19risk factors are still unclear many previous studies investigated that there is a considerable proportion of patients with underlying conditions(Chen et al., 2020). The most usual and common underlying disease was hypertension (14.9%), diabetes

mellitus (7.4%) (Guan et al., 2020), in addition to cardiovascular disease (Wang et al., 2020).

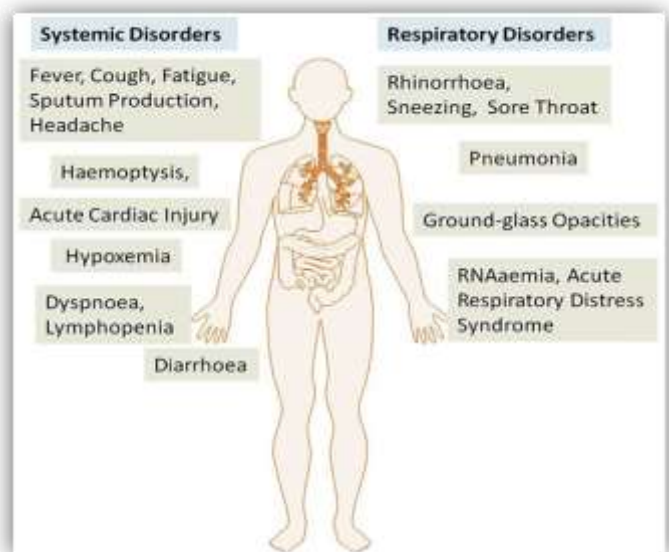


Fig 6. The main respiratory and systemic disorders caused by COVID-19 infection (Rothan and Siddappa, 2020).

Emergency symptoms of a patient suffering from COVID-19 including confusion, persistent chest pain or pressure, difficulty breathing, and bluish face or lips, and difficulty walking (Laiet et al., 2020). Less commonly, upper respiratory symptoms may be seen, like sneezing and sore

throat, in addition to nausea, vomiting, and diarrhea (Hessen, 2020). In March, Chen et al., (2020) cited that “there was investigation proposed that loss of the sense of smell (anosmia) may be seen among patients with mild disease”. In more severe cases, the infection could result in severe acute respiratory syndrome, pneumonia, multi-organ failure, kidney failure, and death (Hui et al., 2020). As reported by WHO in those patients who had severe symptoms, the time required from symptom manifestation to needing mechanical ventilation demand is eight days (World Health Organization [WHO] 2020) (Fig. 6).

Transmission

The novel coronavirus emerged from the Hunan seafood market at Wuhan and rapidly spread to more than one hundred countries. Poor screening of national passengers played a major role in virus expansion in many countries. The sequence-based analysis suggested bats as the key reservoir. Besides bats is the natural reservoir of many RBD, indicating direct human transmission. However, spike glycoprotein involved DNA recombination which featured SARS-CoV with the RBD of another Beta CoV, and that may be the causes for rapid infection and transmission (Adnanet et al., 2020). Meanwhile, SARS-CoV-2 is similar to the SARS-CoVs concerning the whole genome sequence. The main route of SARS-CoV-2 transmission was supposed to be the direct contact with intermediate host animals and eating wild animals. Human-to-human transmission of SARS-CoV-2 occurs mainly between people who are intimately contacted with incubation carriers or patients (Guan et al., 2020). However, in cases from many regions, it has been observed that SARS-CoV-2 had been mutated in China patients basing on analyzed the genotypes of COVID-19 (Zhanget et al., 2020). Many types of research as that done by Zhouet et al., (2020) reported that no significant difference in viral load in symptomatic and asymptomatic patients suggested the chance of virus transmission from asymptomatic patients who spreading the virus and can be easily neglected in epidemic prevention. The pre-symptomatic transmission was estimated between 48% and 62% (Ganyani et al., 2020). The pre-symptomatic transmission was considered (4 to 4.6 days) proposed that many secondary transmissions would have happened when symptomatic patients are diagnosed and isolated (Nishiura, Linton and Akhmetzhanov 2020). The virus is very contagious when people are symptomatic (WHO, 2020). The WHO (2020) and the CDC (2020) cited that “the COVID-19 is primarily spread by small droplets when people coughing or sneezing with distance being one to three meters. Furthermore breathing out, when talking may also bring out respiratory droplets suggested the virus is not usually airborne (van Doremalen et al., 2020). Some additional vehicles were the direct contact with biological materials such as feces or saliva (To et al., 2020). After being produced and under gravity a ~5 μm diameter human droplets rapidly fall to the ground (Atkinson et al., 2020), though human respiratory droplets are considered as the largest source of infection. It may also spread when one touches a contaminated surface. However, the virus survives for hours to days on surfaces (CDC, 2020), while the virus stays three days on

stainless steel and plastic and for up to four hours on copper (National Institutes of Health, 2020). This, however, varies based on temperature and humidity. Fei et al., (2020) demonstrated that women appear to be less risky than those with chronic obstructive pulmonary disease (COPD), hypertension, and cardiovascular diseases. Furthermore, elderly people more than seventy years old, with underlying conditions like hypertension, diabetes, chronic respiratory disease, cancer, and people with cardiovascular disease are at higher risk to have severe COVID-19 disease and even death. Higher ACE2 gene expression may be associated with high severity of SARS-CoV-2 infection. In lung tissues, it has been investigated that ACE2 expression rises with age, and with many types of antihypertensive drugs used (Cai, 2020). Smokers are also considered highly susceptible to COVID-19 (Neil et al., 2020). Mullins, Evans, Viner, O'Brien, and Morris (2020) cited that “pregnant women seem to have similar clinical symptoms as non-pregnant patients with COVID-19 but less lethal for pregnant women than severe acute respiratory syndrome (SARS) (15% case fatality risk (CFR) in pregnancy) and middle east respiratory syndrome (MERS) (27% CFR in pregnancy). However, no intrauterine transmission has been recorded, but optional Caesarean section deliveries area precautionary method to avoid perinatal transmission of the disease (Chen et al., 2020). There is limited evidence regarding severe adverse outcomes like stillbirths, miscarriage, fetal distress, and preterm birth. No pregnancy losses (Liu et al., 2020). However, Wanget al., (2020) cited that “a COVID-19 neonatal case has been confirmed with the unclear mode of transmission, while Zhu et al., (2020) reported that a confirmed maternal infected case has negative laboratory results for COVID-19 for a delivered neonate. Fortunately, the virus has not been found in breast milk (Chen et al., 2020). Meanwhile asymptomatic cases in infants and children have been investigated (Lu et al., 2020). Pathophysiology of COVID -19 Respiratory droplet and direct contact with patients infected with SARS-CoV-2 is the main transmitted route (General Office of National Administration of Traditional Chinese Medicine [GONATCM], 2020). Primary viral replication takes place in the upper respiratory tract, pharynx, and nasal cavity mucosal epithelium, in addition to more multiplication could occur in lower respiratory mucosa and gastrointestinal tract mucosa (Xiao et al., 2020) and the manifestations could cause mild viremia. However, infections could be controlled at this point giving rise to an asymptomatic situation (Huang et al., 2020). Then from the lungs, the virus enters the peripheral blood result in viremia. This virus also invades and attacks the target organs that express ACE2, like the gastrointestinal tract, kidneys, and heart (Dan et al., 2002). Meanwhile, a considerable determinant for the pathogenesis of SARS-CoV-2 infection is the binding of the virus with human cell receptors (Ge et al., 2013).

Invading the human respiratory system by this virus, resulting in the major pathogenesis of the pandemic COVID-19 contagion such as severe acute pneumonia associated with the occurrence of ground-glass opacities, in addition to acute heart damage (Huang et al., 2020). However, the first report was done by Xu et al., (2020) who cited that “pathological findings from cases with a severe COVID-19 revealed a

cellular fibromyxoid exudates and pulmonary bilateral diffuse alveolar damage. The right lung manifests the formation of the hyaline membrane which marked the (ARDS). While the left lung tissue exhibits pulmonary edema combined with the formation of hyaline membrane, indicating the early phase of ARDS. In both lungs, it is obviously demonstrated the interstitial mononuclear inflammatory infiltrates, which lymphocytes are greatest in number. Besides, multinucleated syncytial cells characterized by atypical pneumocytes enlargement with large nuclei, prominent nucleoli, and amphophilic granular cytoplasm, were distinguished within an intra-alveolar space, which suggested viral cytopathic alterations. However, pulmonary pathological findings are quite similar to those seen in severe acute respiratory syndrome (SARS)(Ding et al., 2003)and MERS (Ng et al., 2016). Furthermore computerized (or computed) tomography (CT) of the thorax showed bilateral multilobar ground-glass opacities with posterior or peripheral distribution, accompanied consolidation was observed especially in the elderly people, while septal and pleural thickening, bronchiectasis, cavitation, and subpleural implication are less common. However, a pleural and pericardial effusion seems to be rare (Salehi, Abedi, Balakrishnan and Gholamrezanezhad 2020). Tremendous mucus secretion was observed in both lungs from death cases with COVID-19; this investigation is unlike those from SARS and MERS (Liu et al., 2020). Guan et al.,(2020)investigated in their work that the SARS-CoV-2 found in the patients' feces may be because the virus enters the blood from the lungs and then transports from the blood to the intestines (Wanget al.,2020). Lately, testicular tissues have been investigated to have potential pathogenicity of the SARS-CoV-2, which implying anxiety about young patients' fertility(Fan, Li, Ding, Lu and Wang 2020), other patients with COVID-19 have shown acute liver disease, kidney failure, and heart injury(Huang et al., 2020). However, moderate microvascular steatosis was demonstrated in liver biopsy, which might result from either infected with SARS-CoV-2 or drug users. In the heart tissue, a few interstitial mononuclear inflammatory infiltrates were present, suggested that SARS-CoV-2not directly causes cardiac damage (Xu et al., 2020). Abnormal respiratory findings were observed in patients diagnosed with COVID-19, such as higher levels of pro-inflammatory cytokines and increased leukocyte numbers (Lei, Li, and Qi 2020). Significantly high blood levels of chemokines and cytokines were investigated in these patients comprising; IL1- β , IL1RA, IL7, IL8, IL9, IL10, IFN γ , basic FGF2, GMCSF, GCSF, TNF α , IP10, MCP1, VEGFA, MIP1 α , MIP1 β , and PDGFB. Huang et al., (2020) reported that some of the severe COVID-19 cases that were registered from the intensive care unit exhibit elevated levels of plasma pro-inflammatory cytokines comprise IL2, IL7, IL10, TNF α , GCSF, MCP1, MIP1 α , and IP10 which is the cause to boosts verity of this disease.

Host immune response

Acute respiratory disease is a life-threatening lung situation because it deprives the lungs of receiving enough oxygen, and prevents enough oxygen in circulation, thus is considered a major cause of most respiratory troubles death, and acute lung

damage (Thompson, Chambers and Liu 2017). Many previous studies investigated that genetic susceptibility as well as inflammatory cytokines as the most cause of ARDS. More than forty candidate genes involving ACE2, tumor necrosis factor (TNF), interleukin 10 (IL-10), and vascular endothelial growth factor (VEGF) in addition to other genes have been observed to be linked with the adverse outcomes of ARDS (Meyer and Christie 2013).Furthermore high levels of plasma IL-6 and IL-8 were also investigated to be associated with increased incidence and outcomes of acute respiratory disease (Thompson et al., 2017). Alexopoulou, Holt, Medzhitov, and Flavell (2001) as well as Wu and Chen (2014) reported that the immune response is essential for the control of CoV infections, but it can also result in immune pathogenesis accompanying with the immune response out of control. However, the viral RNAs, as pathogen-associated molecular patterns (PAMPs), are detected by the pattern recognition receptors (PRRs).Mostly, Toll-like receptor (TLR) 3, TLR7, TLR8, and TLR9 sense viral RNA and DNA in the endosome. Takeuchi and Akira (2009) confirmed that the virus-cell interactions result in a varied set of immune mediators against the virus invasion. Specific and innate immunity is required in a precise regulation to get rid of the virus otherwise it will cause immune pathology (Liu et al., 2020). Also, further clinical results in uncontrolled pulmonary inflammation found exuberant significant inflammatory responses during SARS-CoV-2 infection. The cellular damage and rapid viral replication, virus-induced ACE2 down-regulation and shedding as well as antibody-dependent enhancement (ADE) are responsible for harmful and aggressive inflammation resulted from infected with SARS-CoV-2(Fu, Cheng and Wu 2020). However, Yang, (2020) reported that the initial onset of rapid viral replication might result in tremendous epithelial and endothelial cell death and vascular leakage which triggers the exuberant pro-inflammatory cytokines and chemokines production. Loss of pulmonary ACE2 function is suggested to be concerned and linked to acute lung injury (Imai, Kuba, and Penninger (2008).Fu et al.,(2020) explain the reason that ACE2 down-regulation and shedding causes dysfunction of the renin-angiotensin system (RAS), and further boost and increase inflammation, and can lead to vascular permeability. Acute Respiratory Distress Syndrome(ARDS) is the common immune pathological incident for SARS-CoV-2, SARS-CoVas well as MERS-CoV infections (Xu et al., 2020).Several researchers reported that the main mechanisms for ARDS is the cytokine storm, the fatal uncontrolled systemic inflammatory response caused by the release of considerable amounts of pro-inflammatory cytokines (TNF- α , TGF β , IFN- α , IFN- γ , IL-6, IL-12, IL-18, IL-33, IL-1 β , etc.) and chemokines (CCL2, CCL3, CCL5, CXCL8, CXCL9, CXCL10, etc.) by immune effector cells in SARS-CoV infection (Channappanavar and Perlman 2017) (Cameron, et al., 2008). An anatomy report of COVID-1 pneumonia cadaver indicating that COVID-19 gives rise to an inflammatory response in the lower respiratory tract and caused lung injury. However, the virus invades the respiratory mucosa then infected other cells, triggering a series of immune responses and releasing cytokine storms in the human body, which might be accompanied by the critical situation of COVID-19 patients (Guo et al., 2020). Xu et al.,(2020)mentioned that the cytokine storm will trigger a

severe attack by the immune system to the body, result in ARDS and various organ failure, and eventually causes death in a patient with severe SARS-CoV-2 infection, just like SARS-CoV and MERS-CoV infection. Significantly high blood levels of plasma pro-inflammatory cytokines and chemokines were noted in patients with COVID-19 infection that included IL-1 β , IL-1RA, IL-8, IL-9, basic FGF2, MIP1 β , PDGFB, and VEGFA (Huang et al., 2020). Cytokine storm due to too much release of tumor necrosis factor-alpha (TNF- α) and interleukins (IL)-2, IL-6, IL-7, and IL-10 has been investigated (Guo et al., 2020). Inflammatory cytokines such as IL-6 also increased significantly; which lead to more aggravation of the disease around 7-14 days following the onset of the COVID-19 infections (Ling, Lianfeng, Wei and Taisheng 2020). It has been supposed that after a viral invasion, lymphocyte sequestration in peripheral blood leads to lymphocytopenia. An increased level of lymphocytes occurs during recovery is because of recirculation of lymphocyte between peripheral blood and tissues (Xie et al., 2006), while the production of SARS-specific IgG antibodies rises in the late acute stage about two weeks and continue to increase gradually throughout the disease (Chang et al., 2020). Furthermore many studies have been investigated that lymphopenia is a common characteristic feature of COVID-19 indicating a critical factor concerning the severity and mortality of infected patients with COVID-19 (GONATCM, 2020). As reported by Fuet al., (2020), who reported the mechanism of antibody-dependent enhancement (ADE) has been proposed lately. ADE can boost viral cellular uptake of the infectious virus-antibody complexes after their interaction with Fc receptors (FcR), or other receptors, resulting in enhancement of the infection of target cells (Takada and Kawaoka 2003). The interaction of FcR with the virus-anti-S protein-neutralizing antibodies (anti-S-IgG) complex might facilitate the inflammatory responses as well as the continuation of the viral replication in the lungs of patients (Fuet al., 2020). The sustainable presence of IgG makes the patients acquire the immune function after infection. Recovering patients possessed sustained and high levels of S protein-specific neutralizing antibody responses, essential in determining disease outcome (Cao et al., 2010). The IgG level of mild cases was significantly higher than that of severe cases. After a progression of the disease, patients may have an increased level of TNF- α and IL-8, which reach a peak in the early stage of recovery (Stockman, Bellamy and Garner 2006). Ling et al., (2020) reported that "in the pneumonia phase (acute phase), if patients have an effective immune function and no more underlying diseases, the virus can be suppressed effectively, then enter the recovery phase. But in the case of the elderly, or patients with impaired immune function and has other basic diseases like diabetes and hypertension, the immune system couldn't control the virus in the pneumonia phase (acute phase) effectively. In this situation, the patient will be in a severe or critical state. Furthermore, non-survivors had higher levels of neutrophils, blood urea nitrogen, creatinine, and coagulation parameters such as D-Dimer than survivors. Besides chest computerized tomography (CT) suggested the expansion of lung lesions. Li, Chen, and Xu (2003) investigated that antigen could subsequently stimulate the body's humoral immunity in addition to cellular immunity, which is mediated by virus-specific B and T cells. Recently

there are several kinds of research concerning the cellular immunity of coronavirus. The latest report demonstrated that the patients infected with SARS-CoV-2, the number of CD4+ and CD8+ T cells in the peripheral blood is reduced significantly, whereas its status is excessive activation, as indicated by high level of HLA-DR including (CD4 3.47%) and CD38 (CD8 39.4%) double-positive fractions. Peripheral CD4 and CD8 T cells revealed a reduction and overactivation in a severe patient. Several types of research also determined the high concentrations of pro-inflammatory CD4 T cells and CD8 T cells (the cytotoxic granules) indicating antiviral immune responses and hyperactivation of T cells Xu et al., (2020). In addition to abnormal respiratory findings patients infected with COVID-19 showed higher leukocyte numbers (Lei et al., 2020).

Diagnosis

Because of the high transmission of the SARS-CoV-2, its incubation period of 2-14 days, and the propinquity of its symptoms to the common cold (Tang et al., 2020), early and rapid diagnosis of the infection is essential to prevent extension and the spreading of infection and assists the patients to start the treatment faster and to ensure timely isolation the infected patients from asymptomatic, healthy and other pathogenic infections. No drug or vaccine has yet been confirmed to treat patients with coronaviruses, and new interventions require months to years to develop (Li et al. 2020), so early diagnosis and isolation, are the key to success in COVID-19 (WHO, 2020). The clinical symptoms of patients infected with SARS-CoV-2 are highly atypical comprises sneezing and coughing, fever, dyspnea, and viral pneumonia. Therefore, additional examinations and epidemiological history are essential for the diagnosis of COVID-19. Clinical diagnosis of COVID-19 is mainly dependent on clinical manifestations, epidemiological history as well as some auxiliary examinations, like nucleic acid detection and CT scan, enzyme-linked immunosorbent assay (ELISA) and blood culture in addition to immune identification technology of IgM/ IgG (Li and De Clercq 2020). Observe the virus in the stool, urine, and blood samples could confirm that this virus can also infect the digestive system, the urinary system, and the hematological system. Techniques could be used to detected changes, injuries, and lung abnormalities in patients which results from changes in factors and blood cells caused by SARS-CoV-2 (Mahdi et al. 2020). However, previous works confirmed that there are asymptomatic patients infected with SARS-CoV-2 (Bai et al., 2020). These patients can spread the virus and may be easily neglected in epidemic prohibition. So it is necessary to identify asymptomatic patients with COVID-19. Contact history and careful monitoring of the natural course of the disease may be the only way to identify asymptomatic patients. Meanwhile asymptomatic patients or patients with mild COVID-19 symptoms may not receive diagnosis nor require health care, which leads to an underestimation of the COVID-19 burden (Lai et al., 2020). While patients suspected of infection with SARS-CoV-2 usually go to health centers with respiratory symptoms like a fever over 38.5°C, dry cough, and shortness of breath (Cao et al., 2020; WHO b, 2020). In fact with confirmation by real-

time RT-PCR assay, all patients were diagnosed as having severe COVID-19 according to the WHO(WHO c, 2020) and the Guideline of Diagnosis and Treatment of COVID-19 of National Health Commission of China (NHCC),2020.

Molecular study of COVID- 19

PCR-based method

Molecular studies are indispensable to identify the causative agent (Zhang et al.,2020). Balboni, Gallina, Palladini, Prosperi, and Battilani (2012), cited that “polymerase chain reaction (PCR) is an enzymatic method to produce numerous copies of a gene by separating the two strands of the DNA containing the gene segment, marking its location with a primer, and using a DNA polymerase to assemble a copy alongside each segment and continuously copy the copies”. PCR is widely used to amplify minute quantities of biologic materials to provide adequate specimens for laboratory study (Uhlenhaut et al.,2012). The PCR-based method has begun to become a routine and reliable technique for detecting coronavirus. In this technique, coronavirus RNA is transferred into cDNA by reverse transcription (Adachi et al.,2004). Then the PCR is performed and followed by the detection of the PCR product through specific detection instruments. Gel visualization and sequencing after PCR are the conventional methods for the detection of coronaviruses (Setianingsih et al.,2019). But these methods are not commonly used in clinical samples because of their time-consuming process and high cost. The real-time reverse transcription-polymerase chain reaction (rRT-PCR) based technique is currently used to confirm cases with SARS-CoV-2(WHO, 2020).

The test is performed on respiratory specimens such as nasopharyngeal swab or sputum (CDC, 2020), broncho-alveolar lavage, bronchial aspirate. Peng et al.,(2020) improved in their work (using different samples of patients as blood, urine, anal, and throat swabs tested by RT-PCR and screening of virus in all samples)that this virus can infect all respiratory, digestive, urinary, and hematological systems, which indicates that sampling from different parts of the body is recommended and clinical signs in all body parts should be taken into account when diagnosing SARS-CoV-2. Results using this technique are generally obtainable within a few hours to 2 days (Curetis Group Company Ares Genetics (CGCAG) and BGI Group). Because of the advantages of rRT-PCR as a specific and simple quantitative assay, this technique is favored currently for the detection of coronavirus (Wan et al., 2016). Furthermore, real-time RT-PCR which helps much for the diagnosis in early infection is more sensitive than the conventional RT-PCR assay (Noh et al., 2017).

Some patients show unusual symptoms of SARS-CoV-2 infection in its first levels (Qian et al., 2020). For this reason, it is so important to confirm and identify the causative agent using molecular studies various specimens such as throat swab and rectal swabs are tested using real-time reverse transcriptase-polymerase chain reaction testing (RT-PCR) for the molecular study of 2019-nCoV. However, the results performed on throat swabs and rectal swabs of patients with

confirmed 2019-nCoV show that the virus can be detected in both samples (Zhang et al.,2020). Study results of Qian et al.,(2020) investigated that the anal swab was positive even in patients whose oral swab was negative after numerous experiments. This researcher improved the importance of anal swabs in the effective detection of infection with SARS-CoV-2. Generally, RT-PCR remains the primary assay for diagnosing COVID-19 among the different diagnostic techniques available. The RT-PCR methods to diagnose COVID-19 mainly targets different combinations of the open reading frame (ORF), nucleocapsid (N), envelope (E), spike (S), and RNA-dependent RNA polymerase (RdRp) genes(Binnicker, 2020). Yujian and his colleagues (2020) also reported that the use of RT-PCR technology to detect SARS-CoV-2 nucleic acid is a highly sensitive technique and an effective method to screen the SARS-CoV-2 virus. Despite the RT-PCR method is a highly effective and sensitive technique; false-negative results have still been reported in some COVID-19 patients. These results may occur as a result of insufficient inadequate organisms in the samples resulting from the inappropriate collection, transport, storage, and handling, in addition to laboratory test conditions (Xie et al., 2020). Meanwhile, for SARS-CoV-2, the two commonly used nucleic acid detection technologies are high-throughput sequencing and real-time quantitative polymerase chain reaction (RT-qPCR). There liable identification method for SARS-CoV-2 is high-throughput sequencing of the whole genome and virus blood culture (Zhou et al., 2020). Corman et al.,(2020) cited that the RT-qPCR is the most common, straightforward, and effective method for detecting pathogenic viruses in respiratory secretions and blood. But, the application of high-throughput sequencing technology in clinical diagnosis is limited due to high cost and its equipment dependency. However, the Chinese Center for Disease Control and Prevention (China CDC) recommends the use of specific primers and probes in the ORF1ab and N gene regions for SARS-CoV-2 detection by RT- qPCR. The patient considered having confirmed infection with SARS-CoV-2 when both targets are positive. Chu and his colleagues revealed two 1-step RT-qPCR assays (TaqMan-based fluorescence signal) to detect two various regions (ORF1b and N) of the viral genome separately (Chu, et al., 2020). Depending on the protocol used, number and type of samples collected, the detection of SARS-CoV using RT-qPCR can only attain a sensitivity of (50%- to 79%), depending on the protocol used the sample type, and the number of clinical specimens collected (Yam et al., 2003).Therefore it is very important to confirm the detection rate of RT-qPCR for SARS-CoV-2 infection. On the other hand, RT-qPCR has another scarcity, such as certain biological safety hazards obtained from the retention and operation of patient specimens, cumbersome and inconvenient nucleic acid detection operations, also, to long waiting times for results. Although RT-qPCR is specific, its application in clinical diagnosis is limited because of its false-negative rate which cannot be ignored and could lead to the severe consequences of missed diagnosis (Pan et al., 2020). The application of high-throughput sequencing technology in clinical diagnosis is also limited due to high cost and equipment dependency (Corman et al., 2020).

LAMP-based method

The Loop-mediated isothermal amplification (LAMP) is a new DNA amplification method and has the potential to be used as a simple screening technique by clinicians (Sen and Ashbolt 2011). LAMP is a unique isothermal nucleic acid amplification technique. It's used for the amplification of DNAs and RNA with high performance, specificity, and great sensitivity because of its exponential amplification function and six special aim sequences diagnosed by four unique primers simultaneously (Notomi et al., 2000). Nagamine and his colleagues(2002) reported that the LAMP, the target sequence is amplified at a constant temperature of (60–65 °C) using either two or three sets of primers and a polymerase with high strand displacement activity in addition to a replication activity. Typically, four different primers are used to amplify six distinct regions on the target gene, which increases specificity. An additional pair of loop primer scan further accelerates the reaction (Nagamine, Hase, and Notomi 2002). However, the amount of DNA produced in LAMP is extremely higher than PCR-based amplification. To allows easy visualization by the naked eye or through a simple photometric detection process for little volumes, the amplification product can be detected using photometry, measuring the turbidity caused by magnesium pyrophosphate precipitate in solution as a byproduct of amplification (Mori, Nagamine, Tomita and Notomi 2001). The reaction can be followed in RT-PCR either by measuring the turbidity (Mori, Kitao, Tomita and Notomi 2004) or by fluorescence using intercalating dyes such as SYTO 9 (Njiru et al., 2008). Dyes, like SYBR green, could be used to give a visible color change that can be seen with a naked eye without the need for expensive devices. Dyes molecules intercalate or directly label the DNA, and in turn, can be correlated with the number of copies that exist. LAMP can also be quantitative. Tomita Mori, Kanda, and Notomi (2008) investigated that the detection of LAMP DNA amplification in-tube is possible using manganese loaded calcein which starts fluorescing upon complexation of manganese by pyrophosphate during in vitro DNA synthesis (Tomita, Mori, Kanda and Notomi 2008). In 2016, Arunrut et al. cited that “Another method for visual detection of the LAMP amplicons by the unaided eye was based on the incapability to hybridize with complementary gold-bound ss-DNA. In this way, it could and prevent the conversion of normal red to purple-blue color that would otherwise occur during salt-induced aggregation of the gold particles. A LAMP assay combined with amplicon detection by AuNP can have advantages over other techniques in terms of reduced process time, amplicon confirmation by hybridization, and use of simpler devices with no necessity for electrophoresis equipment, thermocycler, or a UV trans-illuminator. The LAMP techniques fast and do not demand highly-priced reagents or equipment (Enosawa et al., 2003). Generally, Gel electrophoresis was used to detect the amplified products for endpoint detection (Poon et al., 2004).

Because LAMP is isothermal, which eradicates the requirements for expensive thermocyclers, could provide major advantages and used in conventional PCR, it may be a particularly beneficial technique for infectious disease

diagnosis in low and middle-income countries (Macarthur, 2009).

Radiological technique

The radiologic technique, chest computerized tomography (CT) scan, is one of the effective ways of detecting viral infection in suspected individuals, which can be particularly useful in an asymptomatic patient and the diagnosis of infection, it can act as a complementary technique to molecular methods making the diagnosis more effective (Ai et al., 2020). As Xie et al.,(2020) reported that the “in patients with confirmed SARS-CoV-2, radiological images of the lungs could provide comprehensive information about the severity of the infection. Images taken from the lungs of different patients offer various lungs abnormalities of patients such as ground-glass opacities (GGO), centrilobular nodules, consolidation, architectural distortion, vascular enlargement, bronchial wall thickening, crazy paving pattern, traction bronchiectasis, reticulation, and intrathoracic lymph node enlargement in addition to subpleural bands, that cause pulmonary discomfort and require rapid diagnosis and treatment. In 21 patients with confirmed SARS-CoV-2, the most pulmonary injury occurred ten days from the initial manifestation n of symptoms. However, in most pulmonary involvement included consolidation in 91% of patients, ground-glass opacities in 75% of patients are said to be characteristic and crazy-paving patterns in 53% of patients, which threaten patients' life(Pan et al., 2020). Furthermore, Mahdi et al.,(2020) cited that “the radiological assay is the most preferred method which can diagnose the infection accurately and quickly with little false-negatives, that can be effective in protecting the patient's life”.

Computed tomography scan

Computed tomography scan (CT scan) also called X-ray computed tomography (X-ray CT), computerized axial tomography scan (CAT scan), and computer-aided tomography is a cross-sectional image used for diagnostic and therapeutic purposes in different medical disciplines(Figure 7). However, computed tomography scans as a medical imaging procedure utilizing the computer-processed combinations of numerous X-ray measurements that are taken from different angles to produce cross-sectional tomographic images of the specific region of a scanned organ to see internal aspects of the organ without cutting. Medical imaging is the most common application of X-ray computed tomography, its produces data that can be manipulated to explain different bodily structures according to their ability to absorb the X-ray beam. Bartscher, Hilpert, Goebbels, and Weidemann (2007) reported about the principle of computed tomography which is based on creating cross-section images by projecting a beam of emitted photons via one plane of an object from determined angle positions performing one revolution. As the X-rays, the emitted photons pass through the object, some of them are absorbed, others are scattered, and some is transmitted. The process of X-ray intensity reduction including only X-rays that are scattered or absorbed named attenuation. Attenuated X- rays' interactions with the object do not reach the X-ray detector.

Photons transmitted through the object at each angle are collected on the detector that visualized by the computer making a complete reconstruction of the scanned object. The 3D gray value data structure obtained in this way exemplifies the (electron density distribution) in the measured organ or object. For the diagnosis of COVID-19, many clinicians suggested computed tomography scans should be the most essential auxiliary diagnostic technique due to more sensitivity. For the patient with a high documented clinical suspicion of SARS-CoV-2 infection with negative RT-qPCR screening, repeated RT-qPCR tests with chest computed tomography scan may be useful. Furthermore for the chest, the high-resolution CT (HRCT) is important for early diagnosis and assessment of disease severity of patients with SARS-CoV-2 (Pan et al., 2020).



Fig 7. The picture showed a modern CT scanner. The second picture showed an antibody tester, used for example to find SARS-CoV-2 antibodies (www.Google.com)

The typical computed tomography images revealed consolidative pulmonary opacities and bilateral pulmonary ground-glass of the parenchyma, sometimes with a rounded morphology with a peripheral, asymmetric, and posterior lung distribution (Ajlan et al., 2014). However, in CT chest ground-glass opacities are said to be characteristic (WHO, 2020) (Figure 8 and Figure 9)

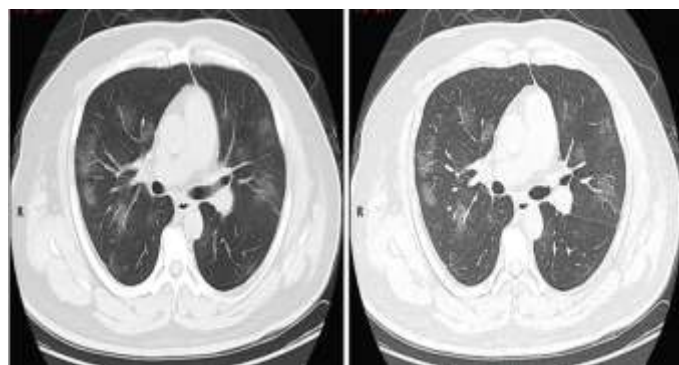


Fig 8: On the right typical CT imaging findings. On the left, imaging examination: multiple patches, grid-like lobule, and thickening of interlobular septa, typical "paving stone-like" signs. ASL(Slice): 6 mm; high-resolution computed tomography(HRCT) (Jin et al.,2020).

Salehi, Abedi, Balakrishnan, and Gholamrezanezhad (2020) investigated that chest radiograph has a little diagnostic value in early stages, whereas computed tomography findings may be present even before symptom onset. Computed tomography is more sensitive than PCR.

Ai et al.(2020)demonstrated in their study that "CT had a higher sensitivity for the diagnosis of COVID-19 as compared with RT-PCR from swab samples in the epidemic area of China". Thus CT scans have a significant clinical diagnostic value for COVID-19, particularly in the high prevalence area of SARS-CoV-2 infection.

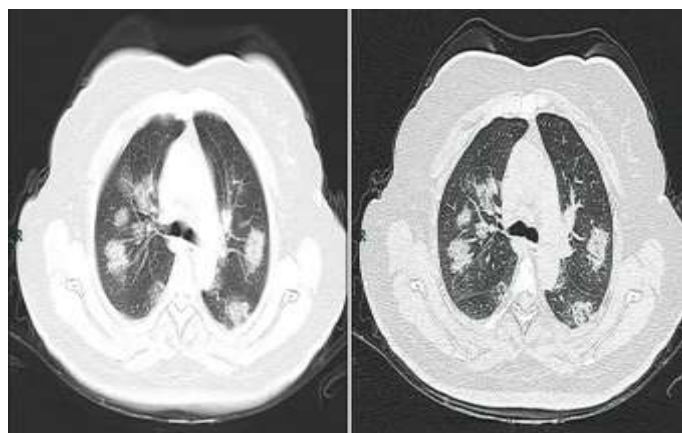


Fig 9. CT imaging of rapid progression stage. Imaging examination: a thin layer CT and high-resolution CT showed multiple patchy and light consolidations in both lungs and grid-like thickness of interlobular septa(Jin et al., 2020).

Serology

It is laboratory testing that detects antibodies produced in response to infection with respiratory COVID-19. The immune response to infection is the production of antibodies including IgM and IgG. However, serology can be used to detect infection inpatient starting seven days or after the first symptoms which have been manifested. This method can be performed in central laboratories. A single sample of peripheral blood is commonly used, and a serial sample can be used to follow the immune response. According to the Food and Drug Administration (FDA) 2020 investigation, one test can gain a result in fifteen minutes. A newer kit was recently developed to detect serum immunoglobulin in a suspected patient which can obtain results in 15 minutes. This assay has a 99% clinical sensitivity rate and a 91% clinical specificity rate. In late March 2020, Europe also improved that this test kit scan detects IgG and IgA antibodies against the virus in blood specimens. The testing capacity is several hundred specimens within hours. Thus it is much faster than the conventional PCR technique of viral RNA. Usually, the antibodies are detectable 14 days after the beginning of the infection (Fellmann, 2020), even in people with mild symptoms that they were ignorant. In this way, it could be recorded the true mortality rate of the disease and how much immunity has been built up in society. Mahdi et al.,(2020) cited that the radiological and serological techniques are the best methods among various diagnosis methods that can help the health centers in the detection of SARS-CoV-2 (Fig. 10).

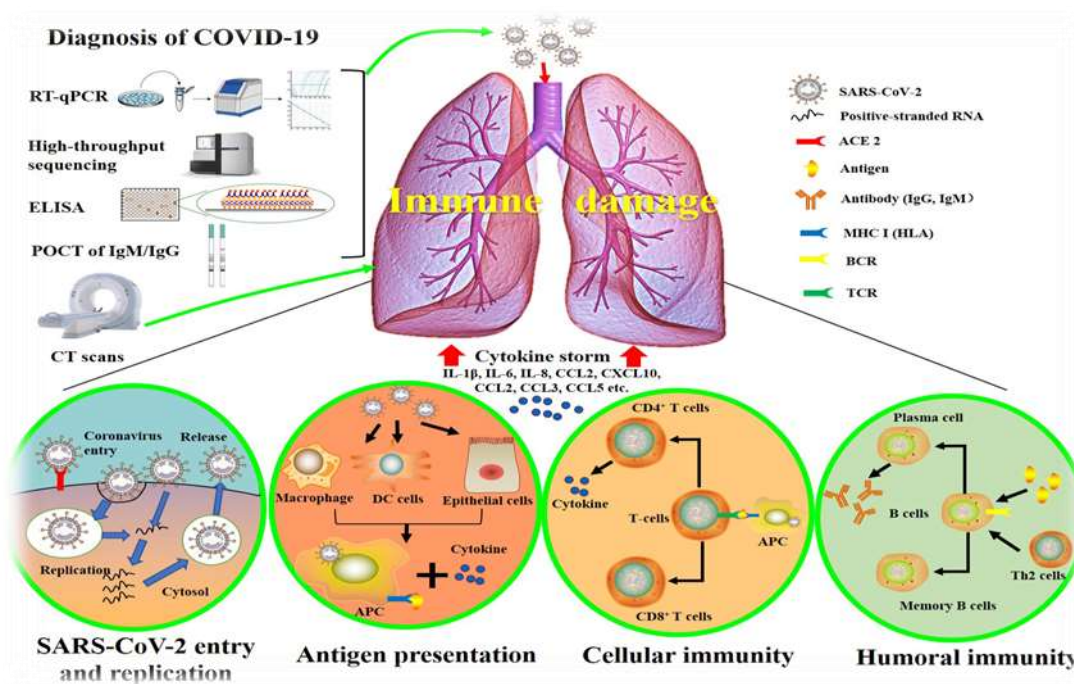


Fig. 10 Show the techniques for SARS COV- 19 (Li et al., 2020).

Treatment

Currently, SARS-CoV-2 is an emerging pathogen that has no effective drug available for treatment. It spreads rapidly and can result in the death of the infected patients (Wu and McGoogan 2020). There are no vaccines or antiviral treatments for the coronavirus family (Chen et al., 2020; Holshue et al., 2020). This has led many researchers throughout the world to investigate the efficacy of drugs such as interferon-alpha and lopinavir which were previously used to treat SARS, along with other novel pharmacological therapies. However, the role of steroids is controversial as it delayed viral clearance (WHO c, 2020). Favilavir, the first anti-viral has been approved for marketing in COVID- 19 pneumonia. Remdesivir and Chloroquine are found to be effective in vitreous investigated by Wang et al.2020). Newer therapies are being tested such as brilacidin, leronlimab (PRO 140), a CCR5 antagonist, and neutralizing monoclonal antibodies along with trials of various other antivirals like ritonavir, lopinavir, oseltamivir (WHO c, 2020). However, plasma from recovered patients is being used to treat patients (Chen, Xiong, Bao, and Shi 2020).

To control SARSCov-19 from global spreading, effective preventive measures should be performed and great effort must be made on the development of vaccine and antiviral drugs. Furthermore, the intermediate host and the mechanism of its cross-species spread should be further investigated.

Conflict of Interest

The authors hereby declare no conflict of interest.

Consent for publication

The authors declare that the work has consent for publication.

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