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Review

Symptoms, epidemiology and diagnosis: A mini-review on coronavirus

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There is worldwide concern about the rapid spread of the Covid19 (COVID-19) pandemic which now affects almost every country in the world. Generating accurate diagnosis of COVID-19 by testing hundreds of thousands of people per day, and the search for effective therapeutics and vaccines are currently the focus of intense research in large numbers of companies and academic institutions around the world. This review will describe the background, origin, epidemiology, symptoms of COVID-19 infection, and its methods of detection. Because of the rapidly changing news on the development of new therapeutic approaches (many of which have already been discarded), and the constantly breaking news - on a daily basis - about the development of vaccines (there are currently 22 separate vaccine programmes worldwide), we will leave the future therapeutic and vaccination options outside the scope of this review. We will address these topics later, once some clarity has prevailed surrounding the large number of putative therapeutic and vaccination options that are currently being explored and an evidence-based approach can be meaningfully applied to interpreting how patient management, and national epidemiological management, can benefit by these emerging breakthroughs.

Key words: Covid-19, corona, diagnosis, epidemiology, cytokine storm, CT scan, SARS.

INTRODUCTION

Coronaviruses are amongst a large group of viruses that may cause disease in animals and humans. There are four main sub-groups of coronaviruses, known as alpha, beta, gamma, and delta. Human coronaviruses (HCoVs) were first isolated in the 1960s from persons with upper respiratory tract infections (Tyrrell and Bynoe, 1965). HCoVs were detected in the alpha coronavirus (HCoV-229E and NL63) and the beta coronavirus (MERS-CoV,

SARS-CoV, HCoV-OC43 and HCoV-HKU1) (Tyrrell and Bynoe, 1965; Shuo et al., 2016). The common human coronaviruses are SARS-CoV, MERS-CoV, and SARS-CoV-2 (COVID-19). SARS-CoV caused severe acute respiratory syndrome (SARS) which emerged in November 2002 (Peiris et al., 2003) and disappeared by 2004 (https://www.who.int/csr/resources/publications). MERS-CoV transmitted from a camel reservoir which was identified in September 2012 and continues to cause sporadic and localized outbreaks (Stalin Raj et al., 2014; Assiri et al., 2013). COVID-19 emerged from China in December 2019 where the first cases of infection belong to people from fish market in the Chinese city of Wuhan (Rothan and Byrareddy, 2020; Zhu et al., 2020; Lu et al., 2020). It is thought that bats are the animal reservoirs for coronaviruses (Giri et al., 2020; Corman et al., 2018; Brook and Dobson, 2015). However, the reservoir animal that transmitted the COVID-19 virus to humans has not been determined so far (Ortiz-Prado et al., 2020).

On March 11, 2020, the World Health Organization (WHO) declared COVID-19 to be a pandemic disease. As of today, July 28, 2020, there are more than 16.7 million global confirmed cases with a death rate of approximately 4% (Li et al., 2020a). These numbers will undoubtedly increase greatly in the coming months, until intercepted by effective treatments, and mitigated through a successful vaccination strategy.

The diameter of coronavirus is approximately 125 nm and it has a relatively large ~31 kb positive-sense single stranded RNA genome. It is a spherical, enveloped, non-segmented and spiky virion which is an assembly of 3 proteins: Spike protein (S), Envelope protein (E) and Membrane protein (M). The name coronavirus has been given because of the crown-like spikes on its surface (protein S) (Li et al., 2020a; Lai and Cavanagh, 1997; Walla et al., 2020).

The Spike protein (S) is heavily glycosylated, which plays a role in enhancing neutralizing antibodies and mediating viral fusion with the host mucosa cell membrane via Hemagglutinin-esterase dimer protein (HE). Studies have shown that angiotensin-converting-enzyme2 (ACE2) is the receptor protein of S protein (Gheblawi et al., 2020). Envelope protein (E) works as a transport channel, whereas M protein is highly hydrophobic (Figure 1).

SYMPTOMS

The symptoms of COVID-19 infections can be classified into systematic disorders and respiratory disorders. Systematic disorders include: fever, dry cough, fatigue, sputum production, headache, hemoptysis, acute cardiac injury, hypoxemia, diarrhoea, dyspnea and lymphopenia. Respiratory disorders include rhinorrhoea, sneezing, sore throat, pneumonia, ground-glass opacities, RNAaemia and acute respiratory distress (https://www.ecdc.europa.eu/en/covid-19/latest/evidence/coronaviruses; Huang et al., 2020).

The incubation period before the symptoms appear was first reported as ~5.2 days (Li et al., 2020b). Others then showed the onset of the symptoms range from 6 to 41 days with a median of 14 days where the age and health background of the patient represent important factors that influence the symptom length and severity of this potentially fatal disease (Wang et al., 2020). This study demonstrated that people older than 70 years of age showed worse symptoms, including health complications of longer duration and greater severity than people younger than 70 years old (Wang et al., 2020). People with pre-existing medical problems such as high blood pressure, heart disease, cancer or diabetes are of high concern since up to 4% of people who have contracted the disease may succumb to it (Liang et al., 2020; Murthy et al., 2020). However, some people become infected yet remain asymptomatic. Most people (about 80%) spontaneously recover from the disease without any need for special treatment (Ortiz-Prado et al., 2020).

It is reported that the infection rate and severity of COVID-19 is relatively low in children compared to adults. The reason behind that could be due to immaturity of ACE2 protein in children. Furthermore, the innate immune system is less mature in children, and thus so is their adaptive immune response. Also, children are more susceptible to respiratory viral infections such as influenza, parainfluenza viruses, adenoviruses, respiratory syncytial viruses, and rhinoviruses. The production of antibodies created during these infections may cross-react with coronaviruses and thus could provide some acquired protection in this way (Li et al., 2020c).

Although the mechanism of action of COVID-19 is poorly understood, the similarity of the virus with the structure with SARS-CoV and MERS-CoV (Weiss and Navas-Martin, 2005; Ren et al., 2020) can offer clues as to the pathogenesis which may in turn help inform strategies surrounding the ongoing development of effective COVID-19 treatments and vaccination approaches (Lai and Cavanagh, 1997; Weiss and Navas-Martin, 2005).

EPIDEMIOLOGY

Coronaviruses are pathogens that target the human respiratory system. Previous outbreaks include both the

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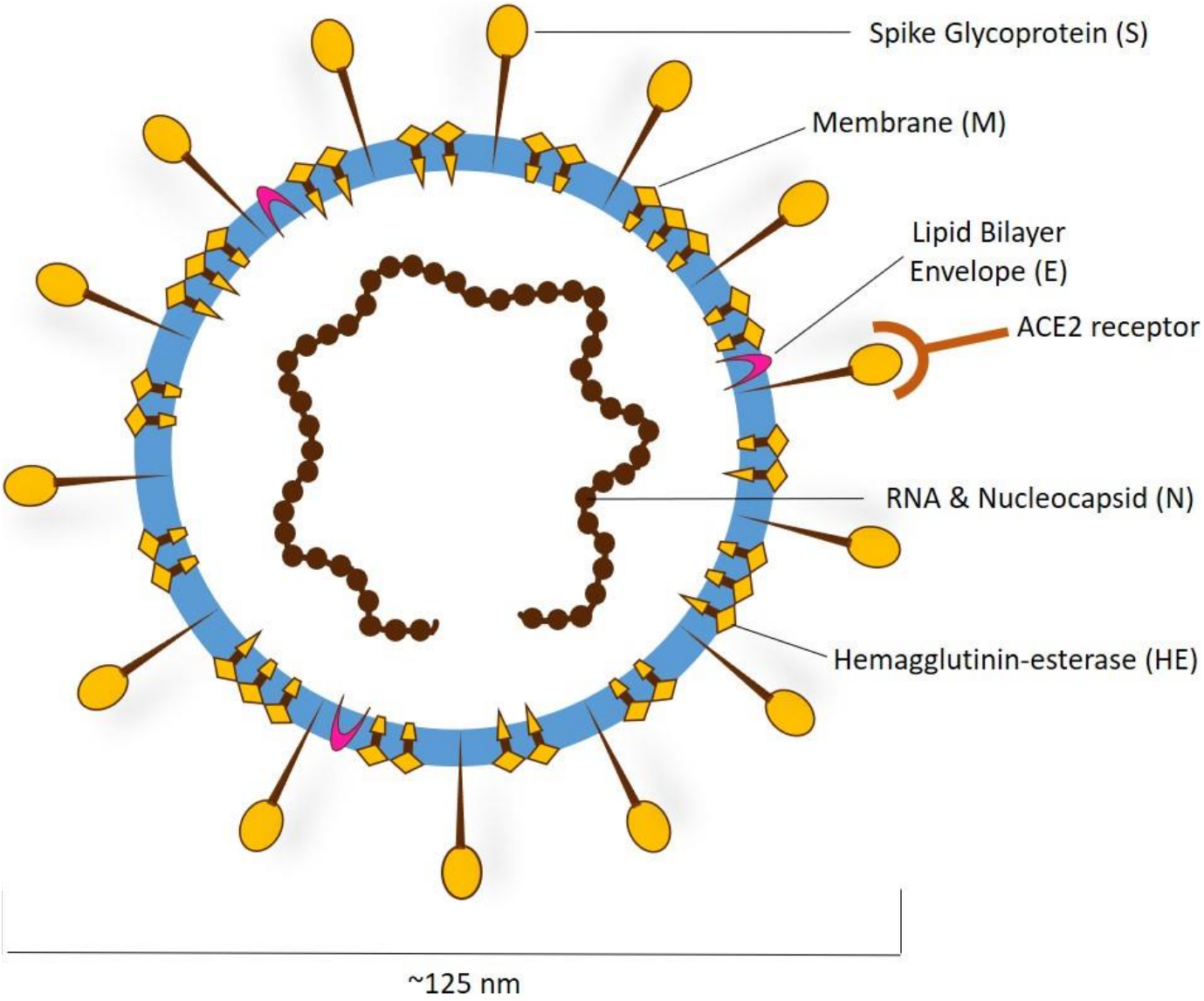

Figure 1. The general structure of coronavirus. The virion is comprised inner and outer layers. The inner layer contains nucleocapsid RNA and phosphorylated nucleocapsid and the outer layer contains phospholipid bilayers covered by the spike glycoprotein trimmer (S). The phospholipid bilayers consists of membrane (M) protein (a type III transmembrane glycoprotein) and the envelope protein (E).

severe acute respiratory syndrome (SARS)-CoV as well as the Middle East respiratory syndrome (MERS)-CoV, both of which were characterised as significant threats to public health. Throughout the second half of December 2019, a small number of patients were admitted to hospitals in China and initially diagnosed with pneumonia of an unknown cause. The infection of these first few patients was epidemiologically linked to a seafood and wet animal wholesale market located in Wuhan, Hubei province, China (Bogoch et. al., 2020; Lu et. al., 2020). Given the estimate of a reproduction number for the 2019 Novel (New) Coronavirus (COVID-19, designated as such by WHO on 11th February 2020) was significantly larger than 1 (estimates at that time were from 2.24 to 3.58), initial reports predicted a potential coronavirus outbreak (Zhao et.al, 2020; Lin et al., 2020).

The first five cases of COVID-19 were reported between 18 and 29th December 2019 (Du Toit, 2020). All five patients were hospitalised with acute respiratory distress syndrome with one patient dead (Ren et al., 2020). By 2nd January 2020, a total of 41 patients were confirmed to have been infected with COVID-19, and fewer than 50% of these patients had underlying diseases such as hypertension, cardiovascular disease and/or diabetes (Huang et al., 2020). These patients were presumed to have been exposed to the virus and infected in that hospital as a result of nosocomial infection, resulting in the conclusion that COVID-19 was

Table 1. Coronavirus population statistics as of **23.9**.2020.

Parameter	Cases of COVID-19	Deaths	Cured
Saudi Arabia	331359	4569	313789
Worldwide	32000000~	~980000	~22000000

Source: Saudi MOH website.

not spread by just one patient to many others. Instead, the increased number of cases was interpreted to have resulted when multiple patients became infected at numerous sites throughout the hospital. Additionally, the only people who were tested at that time were patients that were clinically sick, so therefore it is highly likely that many more people were actually infected. By 22nd January 2020, 571 cases of the 2019-new coronavirus (COVID-19) had been reported in 25 different provinces (districts and cities) in China (Lu, 2020). At this time, the China National Health Commission then reported the details of the 17 patients who had died from the virus. By 25th January 2020 almost 2000 confirmed COVID-19 cases were known to have occurred in mainland China, with 56 confirmed deaths (Wang et al., 2020). An additional report on 24th January 2020 estimated the cumulative incidence of COVID-19 infections in China to be 5502 patients (Nishiura et al., 2020).

As of 29th June 2020, over 16 million individuals worldwide have been confirmed to have been infected with COVID-19 with more than 600,000 of these infections resulting in death (Table 1). Laboratory-confirmed cases of COVID-19 have been reported in every continent other than Antarctica, and in over 180 countries (https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200308).

Over 270,000 COVID-19 cases have been confirmed in Saudi Arabia and this has resulted in more than 2700 deaths as of June 29th 2020.

In May 2020, parameter values to support public health preparedness and planning for the ongoing COVID-19 pandemic were released by the CDC and the Office of the Assistant Secretary for Preparedness and Response (ASPR). The 'best estimates' provided by these two organisations for the transmission of the virus, severity of disease as well as transmission by asymptomatic and presymptomatic individuals have been published (https://www.cdc.gov/coronavirus/2019-ncov/hcp/planning-scenarios.html). As mentioned previously, COVID-19 has a basic reproduction number (R0, otherwise known as R-naught) of 2.5 and of the people who become infected, 3.4% will become hospitalised and approximately 0.4% will die from the disease. Approximately 35% of patients infected with COVID-19 are asymptomatic; however, these patients are just as infectious as those who display symptoms. The average time to symptom onset from exposure to the virus is 6 days and there is a 40% chance of viral transmission occurring prior to the onset of any symptoms (https://www.cdc.gov/coronavirus/2019-ncov/hcp/planning-scenarios.html).

ROLE OF COMPUTED TOMOGRAPHY IN DIAGNOSIS

To date, the most sensitive tool used for confirming an infection with COVID-19 is the reverse transcriptase polymerase chain reaction (RT-PCR) test. Although computerised tomography (CT) has also been heavily used, its precise role for investigating patients with COVID-19 remained initially unclear. One group then reported they found 97% of 601 patients with COVID-19 were accurately diagnosed by CT (Ai et al., 2020). Another group reported that the diagnosis could be confirmed by CT in 50 of 51 patients (98%) compared to only 36 (71%) of these patients when using RT-PCR (Fang et al., 2020). With results of such striking significance, one may conclude chest CT should replace RTPCR in the routine testing for COVID-19, or at least to be the front line tool for screening, especially since CT is a much faster approach because results are immediately available once the scan is complete. However, while reviewing these two publications, Hope et al. (2019) criticized their entire research process and made the point that the consolidation and ground-glass opacity is not solely specific to COVID-19 pneumonia.

Hope et al. (2019) again addressed these methodological flaws in a further publication (Reptics et al., 2020) which repudiated the notion that CT was sufficiently sensitive and specific in diagnosing COVID-19 when used in the absence of an RT-PCR test, and added that doing this 'runs counter to current society guidelines'. They concluded that CT should just be 'reserved for evaluation of complications of COVID-19 pneumonia or for assessment if alternative diagnoses are suspected'.

When using CT, the images seen in cases of pneumonia that are caused by viruses from the same viral family appear essentially the same in those scans because of the similarities in the lung pathogenesis of these related pathogens. Another report showed that about 25% of the early COVID-19 cases detected negative in chest CT scans (Guan et al., 2020). Recently, the American College of Radiology (ACR) recommendations for the use of chest radiography and computed tomography (CT) for suspected COVID-19 infection (www.acr.org/Advocacy-and-Economics/ACR-Position-Statements/Recommendations-for-Chest-Radiography-and-CT-for-Suspected-COVID19-Infection. April 5 2020)

addressed the question of what that may be displaying on a chest CT scan is not specific to COVID-19, and can therefore also be related to other forms of infection. This helped define that a CT scan should not be considered for screening, nor used as front line diagnostic tool for COVID-19, but that chest CT may help in diagnosis of cases with advancing symptoms (World Health Organization, 2020).

CT is an imaging technique that involves a relatively high dose of radiation dose when compared with conventional x-ray techniques. In the early stages of a COVID-19 infection, isolation and supplementary medication are required and what is detected in a CT scan will not change the treatment yet would be exposing the patient to an unnecessary dose of radiation which itself is associated with tangible biological risks (Hall, 2002; Hong et al., 2019). A chest x-ray (CXR) on the other hand, involves exposure to far less radiation, and can be requested, instead of a CT, even on several occasions, to provide continuous information on the status of the lungs (Holshue et al., 2020). If, on occasions a CT scan becomes imperative, that is, if it outweighs patient benefits over patient risks, then low radiation output CT techniques should be performed rather than operating with high (or standard) dose levels (Kalra et al., 2004). By doing this, the radiation exposure concept of “As Low As Reasonable Achievable” (ALARA) can be maintained. Moreover, as COVID-19 is an airborne disease and highly contagious, ensuring a safe application of CT imaging when scanning COVID-19 patients is quite challenging, since any mistakes in following and ensuring good precautionary preventative regimes may result in transmission of the disease to staff and other patients.

ROLE OF ELISA IN DIAGNOSIS

The diagnostic tests used for the detection of COVID-19 infections have been an essential tool in tracking the spread of the disease during the current pandemic. The identification of the genetic sequence of COVID-19 allowed for diagnostic tests specific to SARS-CoV-2 to be developed rapidly (Wang et al., 2014).

Widely utilised to detect and quantify specific antibodies and antigens in samples, enzyme-linked immunosorbent assays (ELISA) share many qualities in common with the radioimmunoassay (RIA) from which they were derived (Gan and Patel, 2013). RIAs were first developed by Yalow and Berson to measure endogenous levels of insulin in plasma, leading to Yalow being awarded the 1977 Nobel Prize (Yalow and Berson, 1996). This assay was further developed resulting in the creation of a novel technique that could be used to detect the presence and quantify biological molecules in minute quantities of sample, which then lead to the analysis and detection of a wide range of other molecules such as proteins, hormones and peptides. Due to concerns about the safety of radioactivity these assays were adapted, leading to the replacement of radioisotopes with enzymes, and thus resulting in the creation of the ELISA (Gan and Patel, 2013). While the use of ELISA could assist in tracking antigen exposure, there are limitations with this approach, in particular the colour change mediated by the enzyme will react indefinitely and hence, if left for a sufficiently long time, the colorimetric change may falsely reflect the quantity of antibody present. Additional limitations include the requirement to generate a reciprocal antibody/antigen in order to detect the antibody/antigen of interest as well as non-specific binding of the antibody/antigen of interest to the ELISA plate thus leading to false-positive results (Gan and Patel, 2013).

Serological testing can also be used to assist in the investigation of an ongoing viral outbreak as well as in the retrospective assessment of the attack rate, or the extent of the outbreak. When validated serological tests are available these could be utilised using paired serum samples (in the acute and convalescent phase) to support diagnosis in the event that nucleic acid amplification tests (NAAT) assays return negative, yet a strong epidemiological link to COVID-19 infection remains (https://www.who.int/publications-detail/laboratory-testing-for-2019-novel-coronavirus-in-suspected-human-cases-2020).

ROLE OF PCR IN DIAGNOSIS

RT-PCR is a regularly used technique for the detection of the causative virus in respiratory secretions from patients suffering from acute respiratory infections. PCR is an enzyme-driven technique used to replicate DNA *in* vitro that can be utilised to produce a large enough quantity of DNA to detect and identify pathogens. As every pathogen has a unique DNA or RNA sequence, these molecules can be utilised as a molecular fingerprint to identify which pathogen is causing the disease in a patient. The clinical application of PCR was revolutionised by the invention of real-time quantitative PCR (qPCR) primarily due to the automation of analysis via removing the requirement for post reaction manipulation. Utilising probes with fluorescent reporter dyes for detection of the conserved genes ORF1ab and RT-PCR is the core technology used to detect the presence of SARS-CoV-2 in samples of the airways of patients. A positive result from one of these highly sensitive tests indicates the presence of viral RNA in the sample; however, a clinical correlation with a patient’s history is also required. It is important to bear in mind that NAAT tests such as RT-PCR, followed by nucleic acid sequencing when appropriate, are considered to be the gold standard for diagnosing COVID-19 as detailed by WHO.

There are many publications describing the process of

amplification of RNA known as reverse transcriptase polymerase chain reaction (RT-PCR) as the gold standard method for the detection of COVID-19 (Xiang et al., 2020). The immunological responses to COVID-19 have also been investigated by many researchers, and there are considerable variabilities in terms of sensitivity and specificity. Other laboratory parameters have been investigated in predicting cases with positive RT-PCR for COVID-19, a higher neutrophil (NEU) count, C-reactive protein (CRP), lactate dehydrogenase (LDH), aspartate aminotransferase (AST), alanine aminotransferase (ALT), and urea levels in serum have all been studied. In addition, patients with a positive RT-PCR have been reported to have a lower white blood cell (WBC) count, and serum albumin levels, compared to others. ALT, CRP, NEU, LDH, and urea showed very good accuracy in predicting cases with positive RT-PCR for COVID-19 as confirmed by the presence of RNA (Mardani et al., 2020).

Furthermore, typical pulmonary features of SARS pneumonia were not evident when studied in one report. Other tests of immunohistochemical staining showed an abnormal accumulation of CD4+ helper T lymphocytes and CD163+ M2 macrophages in lung tissue. Comparably, the case was investigated by SARS-CoV-2 infection RT-PCR and RNA *in situ* hybridization on surgically removed lung tissues (Zeng et al., 2020). The importance of RT-PCR is known for its rapidness, sensitivity and specificity for viral RNA detection as the case of COVID-19. The use of RT-PCR is also an essential tool for epidemiological studies, clinical management, and preventive medicine in general (Yip et al., 2020).

Essentially, to have an efficient RT-PCR method, a carefully selected target for amplification should be examined. In one study, four specific regions in the SARS-CoV-2 genome were identified. This allowed the design of sets of primers to be used for PCR (Yip et al., 2020).

Two other locations, orf1ab and S genes were also used to design primers for the detection assay (Yan et al., 2020). In addition, RdRp gene and E gene were utilized by two groups (Okamaoto et al., 2020; Son et al., 2020). Another group targeted the nucleocapsid (N), envelope (E), and open reading frame 1a or 1b genes to design primers for RT-PCR assay (Chan et al., 2020). The primer sets design should be performed by selecting the target for amplification and the region of the targeted sequence needs to be unique, specifically for COVID-19. This adequately allows RT-PCR assays in diagnostic virology to represent a highly sensitive approach (Yip et al., 2020).

Low copies of the virus may limit its detection; therefore, viral RNA is the best sensitive assay to use (Yip et al., 2020). Most viruses share a common region for the identity of the virus and some unique ones, and some very conserved ones for the strain of the particular virus itself. For this reason it is believed that COVID-19 has a conserved region (as discussed earlier) and studies have shown there is indeed a consistent, conserved region. Whilst the assay must deliver a satisfactory level of reproducibility, one crucial advantage of molecular testing is studying viral clearance assessed by RT-PCR when a drug is used for a cure (Singh et al., 2020). RT-PCR has also been used in the clustering of patients who were infected in a different geographical location to the Singapore study (Yong et al., 2020). A significant percentage (85%) of infected individuals, do not show any clinical symptoms which therefore makes RT-PCR the method of choice for the screening of asymptomatic carriers (Rivett et al., 2020).

Rivett et al. (2020) further studied the clustering of infected health care workers (HCWs) by performing viral genome sequencing for RT-PCR positive individuals who had been screened previously. A dominant lineage B1 was found in many of these HCWs (Yalow and Berson, 1996). The severity of acute disease was confirmed by RT-PCR in one study (Fang et al., 2020). Active disease can be monitored by RT-PCR where an investigator can follow the patients during the course of the viral infection, and some patients of course start to test negative as they recover from their illness (Han et al., 2020).

In the event of a new viral outbreak, a relatively quick establishment of RT-PCR testing for laboratory molecular diagnosis is a vital way to detect organisms of an important pathogenic and infectious nature. Practically, positive rates might be calculated in groups of patients for serological findings which may first be confirmed by RT-PCR (Jacobi et al., 2020). In reality, clinical suspicion of COVID-19 may be assessed by chest radiography (Schiaffino et al., 2020). The purpose here is to overcome the limitations of RT-PCR, especially when negative results have been obtained (Ma et al., 2020). In children with suspected COVID-19, negative results on RT-PCR were first noted in five cases but subsequent testing confirmed they had become positive for the virus.

Chest CT may improve the sensitivity for the diagnosis of COVID-19. However, exposure to radiation should be avoided as much as possible when there is an alternative diagnostic approach, especially for pregnant women and children. Nevertheless, portable chest radiography (CXR) has also been thought to offer a safe and efficient workflow, whilst counteracting possible false negative RT-PCR results. If there were any delay in the availability of RT-PCR to determine the diagnosis of COVID-19, then this would make CXR an attractive choice of approach. Disease severity may also be evaluated by CXR when there is no other way available to assess this (Hu and Wang, 2020).

Imaging has become an indispensable approach for the early detection of COVID-19, and for following the progress and outcome of the illness. Severity of the disease could be evaluated if a chest imaging modality is available (Kalafat et al., 2020). Some investigators

recommend the use of imaging modalities before employing RT-PCR since 60-93% of patients have positive chest computed tomographic findings that are consistent with COVID-19 (Di Micco et al., 2020).

In contrast, the utilization of urine specimens was not found to be informative for the RT-PCR detection of COVID-19. However, RT-PCR-negative patient at day 15 of infection was observed in patients who were positive after taking treatment regimen consisting of hydroxychloroquine (HCQ) and azithromycin (AZ). Therefore, we may conclude that it will probably become normal practice to utilize RT-PCR for the evaluation of the treatment of COVID-19. Further, Million et al. (2020) managed to perform a calculation of fatality rate by applying the RT-PCR assay within COVID-19 laboratory diagnosis.

CYTOKINE STORM

Cytokine storm is a term that indicates uncontrolled and generalized immune response (Ferrara et al., 1993). This term was initially used to describe the events that cause graft versus host reactions in transplantation. The state of cytokine storm is characterized by a powerful, exaggerated activation of the immune system. Cytokine storm is associated with a wide range of infectious and non-infectious conditions (Yuen and Wong, 2005).

One of the major devastating presentations of COVID 19 is acute respiratory distress syndrome (ARDS). This is associated with around 40% mortality and characterized mainly by the presence of bilateral lung infiltrations, and hypoxia. It may present with a wide range of symptoms: pneumonia, sepsis, pancreatitis, and thrombosis. The pathophysiology of this condition involves injury to the alveolocapillary membrane and this results in increased filtration of the lungs and exudation of protein rich pulmonary edema fluid into the airspaces, which eventually leads to respiratory failure (Bhatia et al., 2012).

Data from SARS and MERS-CoV has previously shown that these viruses cause an increased level of pro-inflammatory mediators (cytokines and chemokines) such as interferon γ, interleukin (IL) -1B, IL-6, IL-12, $CXCL_{10}$, and CCL_2. These mediators have been shown to be associated with extensive lung involvement and ARDS (Channappanavr and Perlman, 2017). Similarly, recent reports have shown increased levels of pro-inflammatory cytokines and chemokines in patients with COVID-19 (Huang et al., 2020). This indicates activation of TH1 cells. Of particular interest, is that in COVID-19 there are also increased levels of immunosuppressor mediators secreted by TH2 cells (IL-4, IL-10) (Zhang et al., 2020).

The clinical and laboratory findings in patients experiencing a cytokine storm, include cytopenias (thrombocytopenia and lymphopenia), coagulopathy (low platelet and fibrinogen levels, and elevated D-dimer levels), tissue damage/hepatitis (elevated LDH, aspartate aminotransferase, and alanine aminotransferase levels), and macrophage/hepatocyte activation (elevated ferritin levels). In addition, there may be fever, reduced (or absent) NK activity, elevated levels of CD25, sCD163 and the presence of hemophagocytosis (Crayne et al., 2019).

There are several proposed mechanisms for cytokine storm in patients with COVID-19 some of which are still ongoing. However, some theories for the predisposition to experience a cytokine storm in patients with COVID-19 including:

(1) Impaired viral clearance: Similar to what was thought in SARS and MERS-CoV that the virus exerts some strategies to resist the host defense mechanisms. These viruses are able to produce vesicles that have double membranes and that the virus can replicate inside these vesicles (Snijder et al., 2006). This eventually leads to an impaired immune response against the virus, which will cause additional accumulation of the virus and viral products. In this situation, the PCR test can be negative, yet the patient may experience a devastating effect from the viral inclusion bodies present inside the alveolar cells and macrophages (Xu et al., 2020).
(2) Low levels of type 1 interferon, which are important in viral clearance. It has been noted that patients with MERS-CoV show upregulation of pro-inflammatory cytokines and down-regulation of antiviral cytokines (Chan et al., 2015).
(3) Liu et al. (2019) suggested that antibodies against spike glycoprotein (anti-S-IgG) act as autoantibodies and hence promote a proinflammatory response in the lungs. This response is considered as pathological rather than protective and may act as a mediator of lung injury.

In general, viral escape mechanisms to avoid viral clearance, together with genetic, or acquired defects in the host defense may lead to further accumulation of the virus. This will eventually result in an impaired immune response, and an exaggerated immune activation, that will cause ARDS and multi-organ failure.

The disease course is variable, ranging from asymptomatic to severe life threatening/fatal disease. This is attributed to multiple factors including both genetic and host factors (Rouse and Sehrawat, 2010). This may explain why the mortality is high in some families/regions.

Several studies have shown the correlation between disease severity and inflammatory mediators. In one study, there was a positive correlation between IL-2R and IL-6 and the disease severity. These markers were higher in patients who are critically ill than in patients with a less severe disease course, or in those with no symptoms (Chen et al., 2020). One study reported that COVID-19 patients from ICU have increased serum level MCP-1, granulocyte colony stimulating factor (GCSF), and TNF-α (Huang et al., 2020). This indicates that a cytokine storm

is positively correlated with disease activity/severity in patients with COVID-19. Mortality studies, have reported that elderly patients with ARDS have pulmonary and interstitial tissue damage that was caused by nonspecific inflammatory mediators (Force, 2012).

Implications of understanding the cytokine storm in the specific context of COVID-19:

(1) Cytokines could be the target for treatment via the use of cytokine antagonists and immunomodulators.
(2) Cytokines could be used as markers of disease activity/severity.
(3) Disease monitoring and prediction of deterioration/ mortality.
(4) Individualized treatment should be considered because the presentation of the disease is variable among patients.

CONCLUSIONS

The inflammatory response starts with pathogen recognition and then recruitment of immune cells to the site of infection. Ideally this should ultimately lead to tissue repair and restoration of normal homeostasis. However, local excessive release of cytokines is the decisive factor that leads instead to clinical manifestations and pathological changes. In patients with severe COVID-19, the degree of cytokine increase is also closely related to increased mortality. Therefore, immunomodulation/suppression, and the use of cytokine antagonists, will enhance recovery, and improve survival, in COVID-19 patients. Since December 2019, COVID-19 diagnosis, therapy and research have become areas of great importance. Huge numbers of papers on these topics have already been published. However, further research is needed into the selection of optimal target cells, vectors, and therapeutic methods in order to successfully generate an effective, safe, non-toxic vaccine (or selection of vaccines).

CONFLICT OF INTERESTS

The authors have not declared any conflict of interests.

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