COVID-19: Unraveling 10 Most Significant Answers about The Current Pandemic

Asmaa Tahseen Uthman[1], Noor Natheer Al-Rawi[2], Bidaa Othman[3], Natheer Hashim Al-Rawi[4]

1. Department of Diagnostic and Surgical Dental Sciences, College of Dentistry, Gulf Medical University, Ajman, UAE.
2. Department of Pharmaceutics and Pharmaceutical Technology, College of Pharmacy, University of Sharjah, Sharjah, UAE.
3. Private Dental Practice, Wolfsburg, Germany.
4. Department of Oral and Craniofacial Health Sciences, College of Dental Medicine, University of Sharjah, Sharjah, UAE.

Abstract

People over the world are experiencing a health crisis that hasn't been collectively encountered in hundreds of years. Fears about the COVID-19 are increasing as it spreads from person to person around the world. Millions of people are already infected after eight months of the pandemic. This virus left a scar on the memory of all people around the world as it has affected over 21 millions individuals in more than 200 countries with more than 750,000 confirmed deaths, resulting in labeling it as "public enemy number 1" by many health organizations. SARS-CoV-2 is one of seven types of coronavirus, including the ones that cause severe diseases like Middle East respiratory syndrome (MERS) and sever acute respiratory syndrome (SARS). The other coronaviruses cause most of the colds that affect us during the year but aren't a serious threat for otherwise healthy people. Accordingly, the aim of this paper is to answer the ten most frequently asked questions about the virus identity and its impact on human beings.

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Introduction

Is COVID-19 epidemic, endemic, or pandemic?

With the widespread of the coronavirus (COVID-19) worldwide, it is critical to differentiate among certain terms of identification, like an epidemic, endemic, and pandemic, in order to correctly allocate its risk globally.

When the coronavirus was first discovered, it started as an epidemic, which is a sudden and rapid outbreak of a disease affecting a large number of a particular population or community, and was restricted to Wuhan, China [1].

The word endemic refers to the constant ongoing presence of a disease in a community. However, a pandemic is a disease that has disseminated worldwide over a certain "usually short" period of time. In other words, a pandemic is an epidemic that has spread over multiple continents and spread over the world. The most recent global pandemic is the well-known COVID-19, caused by the coronavirus, which started as an epidemic in Wuhan, Hubei, China[2]. Beginning in December 2019, and spreading to the world within months.

"The number of cases outside China went up by 13-folds, and the number of affected countries has increased three times" says Dr. Ghebreyesus, the general director of The World Health Organization (WHO). As a result, WHO announced the COVID-19 outbreak a pandemic on March 11th, 2020[3]. With more than 21 millions confirmed cases discovered by the mid of August , and more than 750,000 reported deaths. Cases of COVID-19 are still exacerbating at the moment and countries all over the world are taking careful measures to stand against this global pandemic. The question of how lethal COVID-19 is to an infected individual is sought after by many people. Certain rates are important to be considered in determining the severity of the disease, and what should be done accordingly[4].

The Case Fatality Rate (CFR) is the confirmed number of deaths divided by the confirmed number of cases. Furthermore, the CFR in the media is delivered as a measure of the risk of dying, however, it doesn't entirely reflect the risk of death, for two main reasons.

Corresponding author:
Noor Natheer Al-Rawi
Department of Pharmaceutics and Pharmaceutical Technology, College of Pharmacy, University of Sharjah, Sharjah, UAE.
E-mail: noornh1996@yahoo.com

One is that the CFR depends on the people diagnosed with the disease, and in the case of COVID-19, there are many individuals who carry the disease but are not yet diagnosed, so the CFR will tend to overestimate the risk of death. On the other hand, the CFR also counts on the total number of deaths from the disease, however, there are people currently infected with COVID-19 and are on the brink of death, but have not died yet, or others who have died because of COVID-19 , but were listed as though they have died from a different cause. All these factors will trigger the CFR to underestimate the risk of death. Consequently, the case fatality rates alone cannot be used to estimate death at the time being, yet acknowledging its limitations can help us understand the severity of the disease in a better way[4].

The other rate is the crude mortality rate, which is calculated through dividing the confirmed number of deaths over the total population, which gives an idea about the probability that any person in the inhabitants will die because of the disease, infected and healthy ones alike. However, the most significant measure of relevance is the Infection Fatality Rate (IFR). The IFR can be measured by working out the total number of deaths over the total numbers of cases. In the current epidemic, the total number of cases has not been identified yet, accordingly, the total number of deaths will still be a mystery, and this ratio reassembling the missing piece of the puzzle is yet to be found [4].

On the other hand, some people considered coronavirus as a type of common cold, this will take us to the next question.

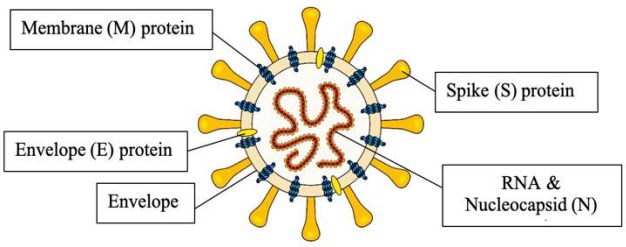

Figure 1. Structure of the coronavirus.

Is it possible that the corona virus is just a mutation of common cold?

COVID-19 is a coronavirus, a member of the Coronaviridae family. The structure of coronaviruses differs from any existing common cold virus. Their membrane contains many viral proteins, spike proteins (S proteins), membrane proteins (M proteins), Envelope proteins (E proteins), and Nucleoprotein (N protein) [3].
Corona in Latin means 'crown', the reason behind this name stems from its structure, as the spikes form large protrusions from the virus surface giving the appearance of a crown, as shown in figure 1.

Severe Acute Respiratory Syndrome-2 (SARS-CoV-2) is the virus responsible for COVID-19.

SARS- CoV-2 achieves cell entry by uniquely targeting human Angiotensin Converting Enzyme 2 (ACE2), this enzyme is expressed in many organs in human beings, like nasal mucosa, lungs, heart, GIT and kidneys. The S protein part of the virus binds with ACE2 to hijack the host cell and use its machinery to produce the disease[3,5].

However, common cold viruses like rhinovirus has 3 subtypes and each has different ways to bind to the host cell, for example they use; ICAM-1 "Intercellular Adhesion Molecule 1" as a receptor, LDL "Low Density Lipoprotein" receptors and CDHR3 "Cadherin-Related family member 3" to mediate cell entry [6].

The symptoms of common colds however include , stuffy or runny nose, coughing, sore throat, sneezing and it's sometimes accompanied by mild fever and aching joints [7]. Meanwhile COVID-19 infection has a wide range of symptoms, and because of that it can cause five different outcomes; mild to moderate cases, severe cases, critical cases and death. COVID-19 is presented with fever, cough and shortness of breath which leads to trouble breathing. In severe cases, Acute Respiratory Distress Syndrome (ARDS) was observed. It is a life-threatening respiratory condition that impairs the ability of the oxygen to get into the lungs and circulation. The reasons why this disease cripples the lungs' function are the following; ACE is highly expressed in the upper respiratory tract, and the primary viral replication site is presumed to occur in mucosal epithelium of upper respiratory tract, with further multiplications in lower respiratory tract [8]. However, some patients have experienced symptoms beyond the respiratory system such as acute liver and kidney failure, diarrhea and heart injury, as ACE is expressed in these organs as well, hence implicating multiorgan involvement [3]. This is what makes COVID-19 different from common cold,

but how does it differ from the flu is what to be discovered next.

Corona verses flu

COVID-19 is a highly contagious and transmissible viral infection.

Many researchers tend to compare this virus with the influenza virus as they both result in some form of respiratory disease, sharing several features, in terms of route of transmission and the symptoms of the patients. However, the coronavirus is very different from the influenza virus as it's far more dangerous and unpredictable. Both the flu and the coronavirus are infectious respiratory diseases that can vary from being asymptomatic or mild to being very severe, and fatal to some patients (Blümel et al., 2009; Nawaz et al., 2020). In addition, both diseases are characterized by fever and a dry cough, which only contributes to their similarity and adds difficulty to their diagnoses. The coronavirus disease may continue to develop even more serious symptoms including severe pneumonia, severe diarrhea, and dyspnea, which makes the disease far more alarming [11].

The coronavirus has an estimated mortality rate of approximately 1-2%, and that percentage is mainly contributed to people with a compromised immune system or with any other respiratory disorders [12]. On the other hand, the influenza virus has a mortality rate of 0.1% which is significantly lower than that of the coronavirus. Both the coronavirus and the influenza virus are transmitted through airborne droplets, as in coughing or sneezing or through direct contact with contaminated surfaces making both diseases very easy to spread [10,11]. This would only mean that proper infection prevention and control measures must be taken, not only for health care professionals but also to the general public especially with the current high and a continuously increasing number of coronavirus cases.

The other biggest difference between the two diseases is the incubation period. The coronavirus has an incubation period of 2 to 14 days, contributing to its ease of spread, as asymptomatic patients could be infected with the virus while spreading the disease to all their surrounding environment before actually knowing that they have contracted the disease. Consequently, adequate testing and screening should be of paramount importance to prevent the further spread of the disease. On the contrary, the influenza virus has an incubation period of 1 to 3 days [9] indicating the presentation of symptoms in a shorter period of time, decreasing the spread of the disease.

The coronavirus patient has been reported to transmit the disease to 2.3 people on average [13], while the influenza patient spreads the disease to 1.3 people on average which yields a much larger chain of spread for the corona virus [14].

The influenza virus can be treated using several antiviral drugs including oseltamivir, zanamivir, and peramivir, all of which aim at shortening the phase of the disease and reducing the symptoms. Vaccine shots for the influenza virus are also available and are recommended for children at a very young age [10]. As for the coronavirus disease, there currently isn't any definitive treatment or vaccine for it, however, researchers and scientists are working against the clock to find a suitable treatment for it. Only Supportive therapy is currently available which includes administration of antipyretic and analgesic, maintenance of hydration, and mechanical ventilation as respiratory support [11].

Having differentiated COVID-19 from both common cold and the flu, the next segment will distinguish closely related coronaviruses of the same family.

SARS, MERS, and COVID-19

Coronaviruses are a well characterized large family of median-sized pathogens, enveloping a large positive-sense single-stranded RNA, typically causing infections of the upper respiratory tract [15], classified into four main categories: alpha, betta, gamma and delta, where the alpha and beta subclassifications are those responsible for human diseases [16].

The story of the corona viruses was first known to mankind through the Severe Acute Respiratory Syndrome-1 (SARS-CoV-1) which emerged from Guangdong, China, in November of the year 2002 and was contained in July 2003. Infecting more than 8000 patients, 774 of them had died, contributing to a Case Fatality Rate (CFR) of 9% [17,18]. Ten years later, the second coronavirus, known as Middle East Respiratory Syndrome (MERS) emerged in Saudi Arabia, infecting a 60 year old man, causing him severe pneumonia. However, the actual outbreak of the

MERS virus didn't happen until two years after that incident. From 2014 to 2016, more than 2000 cases were identified, with 858 deaths, and a CFR of 35% [19]. The third and the most recent outbreak was driven by COVID-19, starting in December 2019, rooting from Wuhan, China, infecting so far more than 10 million cases, and taking the lives of more than 500 thousands, creating a CFR of 4.9%, as provided in figure 2.

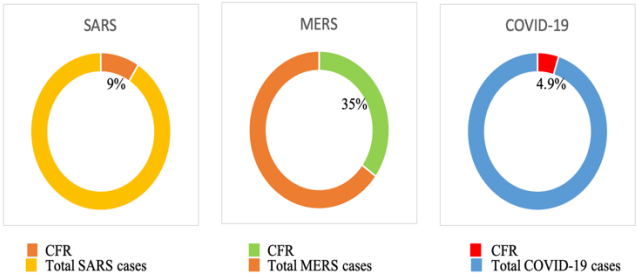

Figure 2. Comparison of Case Fatality Rate (CFR) among SARS, MERS, and COVID-19.

The three coronaviruses are of zoonotic origin, that can easily transmit from animals to humans, employing bats as their primary natural animal host [17]. It has been said that some strains of coronaviruses can't infect humans unless they undergo mutations or recombination in animal hosts. This statement was supported by a recent article stating that "Peri-domestic mammals may serve as intermediate hosts, facilitating recombination and mutation events with the expansion of genetic diversity" [8]. The secret behind becoming lethal pandemics lie in the rapid mode of transmission, primarily from bats, to the intermediate animal, whether it's civet cats in the case of SARS, dromedary camels in the case of MERS [15,17], or pangolins in the case of COVID-19 [3], then to humans, as shown in *figure 3*, and from one human to another via respiratory droplets released from coughs or sneezes. Less commonly, the coronaviruses can also transmit through fomites, fecal transmission and handling of wild animals [20,21]. Nonetheless, SARS has a higher chance of transmission than does MERS [15], yet COVID-19 was found to have the highest transmission, due to the globalization phenomenon [17]. Since the coronaviruses cause pneumonia, similar diagnostic steps were conducted in all three of them, beginning with taking the travel history of the patient, followed by a clinical assessment of the presented patient, radiographic imaging and ruling out of common viral and bacterial pneumonia. Then, certain procedures including the utilization of RT-PCR analysis, cell cultures from the respiratory fluids, or serum IgG antibody analysis were performed [22].

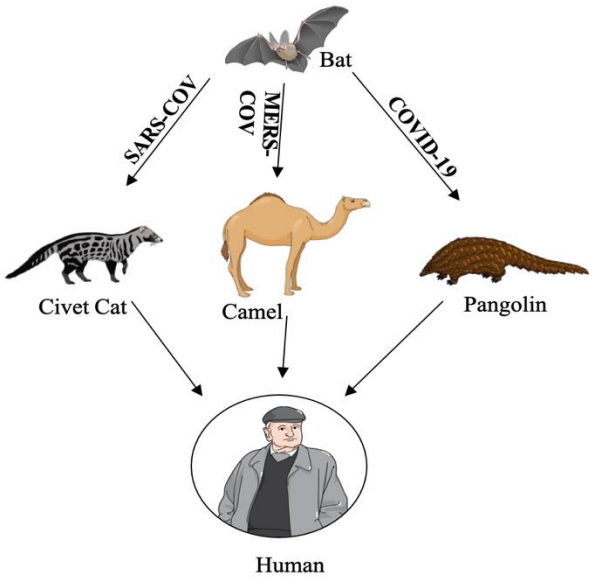

Figure 3. Modes of zoonotic transmission of the coronaviruses to humans.

As for the treatment, antiviral therapies were applied. For instance, combination of Lopinavir and Ritonavir were shown to produce substantial improvements on patients having SARS and MERS, however, no evidence was found to support their use on patients having COVID-19. With COVID-19, Oseltamivir was given to 93% of the patients infected, as an oral administration of a dose of 75mg twice daily, combined with prophylactic antibiotics to prevent secondary infections. Patients with a severe illness were provided with corticosteroids to decrease lung inflammation occurring due to high cytokines levels, with a dose ranging between 40-120 mg/day. To date, no antiviral medication was proven to be effective against COVID-19 [22], the reason may be due to having different strains of COVID-19.

How many human pathological strains of COVID-19 have been identified?

When the virus enters the body, the immune system causes a strong pressure on the virus, which might cause the virus to mutate to surpass the immune system [23]. However, these mutations only cause new variations in functional

sites in the Receptor Binding Domain (RBD) of the virus to compensate the immune system and does not cause new strains of the virus [24]. So how many pathological strains of COVID-19 have been identified?

Genetists have identified 103 SARS-CoV-2 genomes and based on these genes, they have classified the virus into L and S type.
As for the two types, The L type, which is the dominant type, was more common when the outbreak started in Wuhan, China. Then, after January 2020, it started to decrease in the prevalence [24]. Moreover, the L type was placed under heavy pressure as from the human involvement, which made it more aggressive and became more prevalent (%70~) [24]. Some conspiracy theories claimed that the virus emerged from a lab, the following section verifies these allegations.

COVID-19 virus, is it chimeric?

Theories, hypotheses, and some rumors have been spreading about the origin of this emerging viral pandemic. It was suspected that SARS-CoV-2 could be the result of an experiment carried out in the labs. Some people assumed that the virus was leaked from a lab in Wuhan, supporting their claims by a recently discovered bat CoV (RaTG13), showing 96% homology with the SARS-CoV-2. Nevertheless, the human SARS-CoV and the intermediate host palm civet expressed 99.8% homologous recombination, with a total of 202 SNPs found across the genome [25,26]. It was doubtful that RaTG13 CoV is the direct source of SARS-CoV-2, since more than 1,100 nucleotide discrepancies were found between the humans SARS-CoV-2 and the bat RaTG13-CoV, which were dispersed across the genome in a naturally occurring pattern, creating the evolutionary features of typical CoVs [26]. The lack of a clear targeted pattern in the latest viral sequences and a similar relation in a bat mammalian species were the most revealing indicators that the natural evolution was responsible in the formation of the SARS-CoV-2. To specify whether the animal CoVs were linked to the human SARS-CoVs-2, it was important to look for an intermediate host between the humans and the bats. A study of the Relative Synonymous Codon Usage (RSCU) observed that SARS-CoV-2, bat-SL-CoVZC45, and snakes had common synonymous codon usage bias, and hypothesized that snakes might be the intermediate host. No SARS-CoV-2 has, however, yet been identified from the snake [25]. Another study assembled the genomes of the coronaviruses found in sick pangolins, and their results demonstrated a genetically related pangolin coronavirus to both COVID-19 and a group of bats CoVs, in which they found high sequences similarity between them [27]. Phylogenetic analysis did not, however, support the COVID-19 origin from the pangolins. Another analysis of a sample from Malytan pangolins found novel coronaviruses representing two sub-lineages similar to SARS-CoV-2. The similarity in genomes between SARS-CoV-2 and pangolin coronaviruses was about 85-92%, which was lower than that in a bat coronavirus RaTG13 (96.2%). Moreover, the S-protein binding receptor region from one sub linage of the pangolin coronaviruses demonstrated 97.4% similarity in amino acid sequences from that of SARS-CoV-2, much higher than RaTG14 (89.2%). Interestingly, the pangolin CoV and SARS-CoV-2 had the same amino-acid at five essential residues of S-protein RBD, while RaTG13 had only one [25]. The presence of pangolin-CoV near SARS-CoV-2 indicated that pangolins were a possible intermediate host.

These studies postulated that the SARS-CoV-2 was a recombination of two different viruses; one similar to RaTG13, and the other closer to the pangolin isolated virus. This suggested that this virus might be a chimera between the two pre-existing viruses, which has evolved naturally.

Although there is still no evidence available of the possibility of SARS-CoV-2 escaping from a lab but looking into the previous experiences with the corona virus family, it becomes understandable that poor handling by the lab personnel and breaking off laboratory protocols have proved to be the causes of the viruses escaping from the lab. Therefore, continued vigilance to prevent the re-emergence of this deadly virus from laboratories was repeatedly emphasized as live SARS-CoV or SARS-CoV-2 containing materials were handled in a large number of laboratories worldwide.

One of the most important questions that remains unanswered till today is; would our immune system be able to handle this attack?

Ahmadpoor and Rostaing stated “it

seems that the body is unable to produce an adequate adaptive response against this virus" [28]. The virus antigen is presented by antigen presenting cells through MHC I & II to signal the T-lymphocytes, which trigger our body's immune system to start protecting itself. In the cellular immunity, $CD4^+$ and $CD8^+$ T-cells, decrease in number in the blood of patients diagnosed with SARS-CoV, this signifies that the virus had started its attack [29–31]. The dramatic loss of CD4 and CD8 T-lymphocytes is due to impaired Antigen Presenting Cells (APCs) and dendritic cell (DC) function, leading to a compromised elimination of the virus [32].

A sharp reduction in the number of antigen-specific T cells, with 90–95 % of virus-specific T cells undergo apoptosis, [32] this decline allows the virus to protect itself against any defense form the body [31]. For instance, an asymptomatic carrier of this virus would have a mild decrease in the amount of T-lymphocytes; while a symptomatic stage would imply a major decrease in the number T-lymphocytes [33]. This antigen sneaks into the body taking over the healthy cells in the nose, throat and lungs, using these cells as a source to make news viruses [34]. It targets the respiratory system by directly disturbing the respiratory airway epithelium, which stimulates the respiratory dendritic cells to process the antigen, to then migrate to the draining lymph nodes. The production of antiviral cytokines occurs leading to a condition, called the cytokine storm syndrome. This syndrome is a mode of attack that this novel virus uses to cause inflammation. The inflammatory response that occurs is because of the overreaction of the immune system trying to defend itself once SARS-CoV-2 starts attacking, involving a release of inflammatory mediators that trigger the inflammation in the lungs to occur, causing inflammatory-induced lung injury to happen which subsequently leads to pneumonitis, acute respiratory distress syndrome (ARDS), respiratory failure, shock, organ failure which might lead to death [29,35]. At this stage, immunosuppression must happen to stop all this [30]. As previously stated COVID-19 CFR is approximately 5 % which are caused by multi-organ failure especially in elderly people and people with underlying health conditions such as hypertension, cardiovascular disease and diabetes " [29]. This lead us to raise the following .

What is The Prevalence of Comorbidities in the novel Wuhan coronavirus (COVID-19) infection?

Older individuals are at a greater risk for developing Coronavirus infections; this is especially true for elderly patients having underlying systemic conditions such as cardiovascular diseases, diabetes, hypertension, Chronic Obstructive Pulmonary Disease (COPD) that weaken their immunity, causing them to become medically compromised. Wang et. al concluded that hypertension, diabetes, chronic obstructive pulmonary disease, cardiovascular and cerebrovascular diseases are independent risk factors associated with COVID-19 patients [36].

Hypertension, Diabetes, COPD, Cerebrovascular and Cardiovascular diseases show a greater risk of exacerbation with odds ratios of 2.29, 2.47, and 5.97, 3.89 and 2.93 respectively. There was found to be a positive association between those underlying systemic diseases and the development of SARS-CoV-2. However, no correlation was found between liver, kidney diseases, and malignancies with COVID-19 severity [36]. A Study done by Guan et.al [37] found that older individuals are most likely to have one or more underlying comorbidity, eventually leading to severe cases of SARS-CoV-2 infections. In due course of COVID-19, when infections are very severe, the composite end points are reached which consist of admission to the ICU, intensive ventilation, or death, and this risk increases with associated systemic diseases [38]. With the presence of at least one rudimentary comorbidity, hospitalized patients have a greater liability to be admitted to the intensive care unit [39]. Along with many fatal outcomes, the immune system of such individuals drops significantly which can cause various diseases with enteric, respiratory, hepatic and neurological symptoms [37]. However, hyperinflammation due to influx of cytokines may be another cause of death from this dreadful disease.

What is the meaning of cytokine storm, and how does it affect humans during COVID-19 infection?

Evidence proposed that a certain subgroup of severe COVID-19 infected patients might develop Cytokine Storm syndrome, essentially it is an expression of a life-threatening hyperinflammation. Acute Respiratory Distress

Syndrome (ARDS), considered to be the leading cause of mortality, is nothing but a cardinal feature for secondary Haemophagocytic Lymphohistiocytosis (sHLH), which is an underrated hyperinflammatory syndrome, inducing deadly hypercytokinaemia with multi-organ failure. In adult patients, sHLH was found to be triggered by viral infections [40], occurring in 3.7- 4.3% of the sepsis cases [41]. Symptoms, other than the pulmonary involvement of ARDS, include persistent fever, hyperferritinaemia, and cytopenias, presented in around 50% of the patients [42].

The disease severity associated with the COVID-19 infection is established by a cytokine profile reassembling sHLH. It is featured by high inflammatory mediators, like increased interleukin IL-2, IL-7, interferon-γ, inducible protein 10, tumor necrosis factor-α, granulocyte-colony stimulating factor, monocyte chemoattractant protein 1, and macrophage inflammatory protein 1-α [22]. Fatality predictors from a retrospective, multicenter study of 150 confirmed COVID-19 patients in Wuhan, China, incorporated ferritin and IL-6, being significantly more elevated in non-survivors compared to survivors, suggesting that mortality was driven by viral hyperinflammation [43]. Corticosteroids were not the most fabulous option for routine use, as it was believed to aggravate the lung injury associated with COVID-19 infection. Therefore, a more appropriate option of immunosuppression was likely to hold benefits in the management of the hyperinflammation [43]. Analyzing data of a phase III Randomized Controlled Trials (RCTs) of Anakinra, (IL-1 blocker) in sepsis, showed significant elevation in the survival rate, without having a devastating increase in the adverse effects [44]. A multicenter, randomized controlled trial of the drug Tocilizumab (IL-6 receptor blocker), which was licensed for cytokine storm syndrome, has been approved in China, for patients with COVID-19 pneumonia and elevated IL-6 levels [42].

All patients with severe COVID-19 are advised to be screened for hyperinflammation, using laboratory trends of increased ferritin, decreased platelet counts, or erythrocyte sedimentation rate. Furthermore, the H Score11, which generates a probability for the presence of sHLH, to identify the subgroup of patients whose mortality rates can minimize due to immunosuppression. Therapeutic options like steroids, IV immunoglobulin, selective cytokine blockers such as Anakinra or Tocilizumab. In addition to Janus Kinase (JAK) inhibition could minimize both inflammation and cellular viral entry in COVID-19 infection [42].

What is the Molecular immune pathogenesis and diagnosis of COVID-19?

The unique structure of SARS-CoV-2 contains a single-stranded RNA and different proteins, one of which helps infecting the cells, known as the spike protein (s-protein). As the virus enters the body, the S-protein bind to specific receptor known as angiotensin-converting enzyme type 2 (ACE2). Soon after binding, it fuses with the cell, releasing its RNA genome into the cytoplasm, which takes control over the host cell's nucleus to pilot the viral replication process, to have the newly formed viruses eventually bud off damaging the host cell. During this process, the antigens of the virus will be displayed on the surface of APCs. They are presented by the MHC, which is a set of proteins embedded on the APCs' surface to help identify foreign particles, aiding in their recognition by the cytotoxic T-cells [23]. This will trigger an immune response, the non-specific innate immunity, by macrophages, as well as the more specific humoral immunity that acts by producing antibodies. This helps control the virus, inhibiting its spread. However, in severe cases, the immune response is not efficient, and the cytokines accumulate as more cells get affected by the virus, resulting in a "cytokine storm" [24].
Once the body is infected, signs and symptoms will begin to appear, such as high fever, cough, dyspnea, fatigue and even pneumonia. The differential diagnosis includes all types of respiratory viral infections, atypical organisms, and bacterial infections. Therefore, certain tests, like the nasopharyngeal swab tests can be done to rule out some of these diseases, such as influenza A and B. To confirm the COVID-19, epidemiological history and various diagnostic tests are needed to be taken.

Regarding laboratories findings, blood samples were taken from COVID-19 positive patients. These tests showed lymphocytopenia, which was shown in approximately 83% of hospitalized patients. These tests also revealed an elevation of prothrombin time (PT), some inflammatory markers, as well as increase in lactate dehydrogenase, D-dimer, serum alanine

aminotransferase and aspartate aminotransferase. Not only that, but the rising levels of CRP, ferratin and high erythrocyte sedimentation rate were noted [45].

The gold standard for the diagnosis of COVID-19 is the Reverse Transcription-Polymerase Chain Reaction (RT-PCR) test, that helps in the detection of the viral RNA. However, its limited sensitivity can result in false-negative results. Hence, it is advised to make a second confirmatory chest X-Rays and CT scans, as they are more specific and conclusive.

For radiographical findings, chest radiographs taken at the early or mild stages of the disease mostly appeared normal, however, at the initial hospitalization time, 69% of the patients demonstrated abnormal radiographs, then, during their hospitalization period the percentage increased up to 80%, and the findings became more extensive after 10-12 days of symptoms onset. The abnormalities that have been detected were mainly air-spaced opacities that can be described as consolidations or even ground-glassed opacities, with the distribution being bilateral, peripheral, and the lower zone. Some pleural effusions were seen but in a lower percentage as compared to parenchymal abnormalities. Due to the normal image that the radiograph shows in the early and mild stages it's said to have very little diagnostic value [46].

The CT scan on the other hand showed findings of COVID-19 even before the onset of the symptoms, it was also used in the diagnosis of some false-negative cases which resulted from the RT-PCR screening test. The CT scan primary findings showed ground-glass opacities (GGOs) bilateral, subpleural, peripheral, crazy paving appearance (GGOs and inter-/intra-lobular septal thickening), air space consolidation, broncho-vascular thickening in the lesion and traction bronchiectasis [47].

What's more, they described the changes that had been going on in 4 stages: Early stage (from days 0 to 4): normal or GGO images. Progressive stage (from days 5 to 8): GGO and crazy paving appearance . Peak stage (day 9 to 13): consolidation . Absorption stage (day 14 and more): fibrous strips (with improvement in the disease course) [48,49].

As for Pediatric CT, 16% of the studied cases displayed normal CT with no sign of pneumonia, while the rest showed ground glass opacities, similar to what was seen in adults [50].

Also, serological tests can be done to look for the viral antigens or antibodies, and patients with COVID-19 usually present acute serological responses [3]. Currently, IgM/IgG and ELISA kits for COVID 19 are being studied to help in the diagnosis of the disease [32]. Hence, a combination of the aforesaid tests can provide better solutions in the confirmation of the disease and assessing the severity of each case.

How does the coronavirus test work?

Due to the seriousness and rapid spread of the virus, an intense need for rapid diagnosis is required to detect, prevent and contain the virus as soon as possible [51]. These tests help to assist preclinical examinations and aid in the development of medical countermeasures. Previous testing methods for SARS-CoV and MERS-CoV like Nucleic Acid Amplification Test (NAAT) and serological testing were used also for COVID-19.

NAAT test confirms infected patients by detecting the virus genetic material. The first test was designed in Germany. A study designed a candidate diagnostic Reverse Transcription-Polymerase Chain Reaction (RT-PCR) test based on the SARS coronavirus as it was suggested that COVID-19 was SARS-like [51].

The RT-PCR is faster and the most specific and accurate method to track COVID-19 specific genetic material, aiming mainly on the open reading frame (ORF), envelope (E), nucleocapsid (N), and RNA-dependent RNA polymerase (RdRp) genes. The samples are collected from individuals who are suspected via swabs from the back of the throat (oropharyngeal) and the nose (nasopharyngeal) or sputum sample [52], presenting results within 6 hours to 2 days..

RT-PCR makes use of mRNA instead of DNA as the primary template. Reverse transcriptase enzyme provides a complementary single-stranded DNA known as cDNA by using the mRNA template in a technique known as reverse transcription. Then, the single-stranded cDNA is used to create double-stranded DNA using a DNA polymerase enzyme. In each cycle, the amount will be doubled. It usually goes up to 35 cycles in the standardized setup of the RT-PCR. The machine's computer measures the intensity of the fluorescence and presents it in real time on the screen. The signal of the fluorescence increases as copies of DNA are

more produced [53,54].

When the fluorescence goes beyond a certain threshold, the test is confirmed to be positive. If the fluorescence didn't go beyond a certain threshold, this indicated the virus is not in the sample and the person is tested negative. Researchers also count how many cycles would it take to reach the threshold, to predict the infection's severity: the less number of cycles, the more severe the situation is [53,54].

Another type of testing is the existence of coronavirus is serological testing, and it can be used when NAAT is not available or gives a negative result in an area where the possibility of infection is very high. It is a diagnostic identification of antibodies in serum. These antibodies are formed in response to the infection, but this method requires 14 to 28 days to be effective as antibodies need this amount of time to target the virus [51].

After the release of the genome sequence of 2019-nCoV, the tests became very sensitive and specific and aren't reacting with other members of the coronavirus family [51].

Conclusions

It's been established that COVID-19 is a worldwide pandemic, with a CFR of 4.9%, caused by multi-organ failure especially in elderly people and people with underlying health conditions. SARS-CoV-2 enter via ACE2 enzymes to hijack the host cells to produce the infection, and displays antigens on the APCs to trigger an immune response. COVID-19 can have similar transmission pathways, and symptoms in common with the common cold and the flu, but the mechanism of entrance, the severity of the outcomes, and the mortality rates are different. SARS-CoV-2 also differs from its ancestors, the MERS and SARS, in terms of having the highest transmission rate, and a different intermediate animal transmitter. SARS-CoV-2 has 103 genomes, classified to L and S type, with the L type being the predominant. No evidence was found to support the possibility of SARS-CoV-2 escaping from a lab, yet continued vigilance is executed to prevent the re-emergence of deadly viruses from laboratories as live SARS-CoV or SARS-CoV-2 containing materials were handled in a large number of laboratories worldwide. The RT-PCR is faster and the most specific method to track COVID-19 specific genetic material, and samples are collected from individuals who are suspected via swabs from the back of the throat (oropharyngeal) and the nose (nasopharyngeal) or sputum sample.

Declaration of Interest

The authors report no conflict of interest.

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