MINISTRY OF HIGHER EDUCATION

AND SCIENTIFIC RESEARCH

UNIVERSITY OF BABYLON

COLLEGE OF PHARMACY

# GRADUATION PROJECT

# DETECTION OF SOME PARAMETER IN PATENT WITH COVID-19

submitted to the council of the college of pharmacy Babylon university as partial fulfillment of the requirement for the bsc degree of pharmacy

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بسم الله الرحمن الرحيم

اقرأ وربك الأكرم الذي علم بالقلم

علم الإنسان ما لم يعلم

صدق الله العلي العظيم

اهداااء.....

الحمد الله وكفى .. والصلاة على الحبيب المصطفى واهلهِ ومن وفى اما بعد.....

الحمد الله الذي وفقنا لتثمين هذه الخطوة في مسيرتنا الدراسية وجعلها ثمرة للجهد والنجاح ب بفضلهِ تعالى.

اهدي هذا البحث:

الى كل طالب علم يسعى لكسب المعرفة

الى من ارادوا طيب العيش وكرامة المعيشة في وطن حر

الى شهداء ثورة اكتوبر خاصةً وشهداء العراق كافةً

الى الذين ضحوا بالغالي والنفيس من اجل هذا البلد فتوجوا شهداءَ شرفاء كرماء

الى الذين يفرحون بنجاحنا ويساندوننا عند الاخفاق

. إلى من ساندتني في صلاتها و دعائها..... إلى من سهرت الليالي تنير دربي

.إلى من تشاركني افراحي وآساتي ..... إلى نبع العطف والحنان والجمال

إلى أروع إمرأة في الوجود : أمي الغالية.....

إلى من علمني ان الدنيا كفاح ..... وان سلاحها العلمُ والنجاح

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قال تعالى (( ومن يشكرُ فأنما يشكرُ لنفسهِ)) صدق الله العظيم

احمد الله حمدًا كثيراَ طيبًا مباركًا فيه على ما اكرمني بهِ من اتمام هذه الدراسة التي ارجوا ان تنال رضاهُ فلهُ الحمد والشكر اولآ واخراً

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راجين من الله ان نكون قد وفقنا به

والله ولي التوفيق

# CORONA VIRUSES ( COVID -19 )

## Abstract


- Coronaviruses is  a group of viruses that are important human and animal pathogens. In humans the virus causes respiratory infections that include the common cold, which are usually mild, and rarely fatal, It may cause diarrhea in cattle and pigs and in chickens it may cause diseases of the upper respiratory tract.
- Corona viruses were discovered in the 1960s, and the first viruses discovered were the infectious bronchitis virus in chickens and two viruses from the nasal cavity of human patients with colds named human corona virus 229E and human corona virus OC43. Since then other members of this family have been identified including: 2003 SARS coronavirus, 2004 NL63 human coronavirus, 2005 HKU1 human coronavirus, 2012 MERS coronavirus, and 2019-nCoV novel coronavirus, most of these viruses It has a role in causing serious respiratory infection and may even lead to death.
- Coronavirusesis a widespreadviruses known to cause human illnesses ranging from the common cold to more severe illnesses such as Middle East Respiratory Syndrome (MERS) and Severe Acute Respiratory Syndrome (SARS) and the novel coronavirus that caused the 2019-2020 outbreak.
- Severe acute respiratory syndrome coronavirus (SARS-CoV)-2, a novel RNA coronavirus from the same family as SARS-CoV and Middle East respiratory syndrome coronavirus (MERS-CoV), was identified in early January 2020 as the cause of a pneumonia epidemic affecting the city of Wuhan, the capital of Hubei province, from where it rapidly spread across China. After infecting and causing the death of thousands of persons in China, the virus has spread, reaching Italy and other European countries and the USA, with the number of confirmed new cases currently increasing every day


## WHY IS IT CALLED BY THAT NAME?

The name "coronavirus" (Arabic: corona virus, abbreviated CoV) is derived from (Latin: corona) meaning crown or corona, where the name refers to the distinctive appearance of virus particles (freons) that appears through the electron microscope, as they have indentations of surface protrusions, which it a ppears as the king's crown or solar corona[7].

## DEVELOPMENT:

The most recent common ancestor of the alpha corona viruses, beta corona viruses, corona gamma viruses, and corona delta viruses were placed at about 2400 BC, 3300 BC, 2800 BC, and 3000 BC, respectively. Bats and birds - warm-blooded flying vertebrates - appear to be ideal hosts for the source of the coronavirus gene (bats for alpha and beta coronaviruses, birds for gamma and delta coronaviruses) and a suitable environment to support the evolution and spread of the coronavirus[8].

## THE CLASSIFICATION:

- Coronaviruses are enveloped viruses with a positive-sense single-stranded RNA genome, and possess a homologous helical nucleocapsid. The genome of coronaviruses is about 26 to 32 kilobases in size, and is the largest among RNA viruses[9].
- Coronaviruses (and toroviruses) are classified together on the basis of the crown or halo-like appearance of the envelope glycoproteins, and on characteristic features of chemistry and replication. Most human coronaviruses fall into one of two serotypes[9]

## SHAPE OF VIRUS:

- Several proteins contribute to the general structure of all coronaviruses: the spike (S), the envelope (E), the membrane (M) and the nucleocapsid (N). In the specific case of SARS-associated coronavirus, a specific receptor-binding domain in S acts as a mediator of attachment of the virus to its cellular receptor, angiotensin-converting enzyme 2 (ACE2). Some coronaviruses (particularly members of the beta coronavirus subgroup A) also have a protein shortest spike-like is called hemagglutinin esterase (HE)[10].

- Coronavirus virions are spherical to pleomorphic enveloped particles. The envelope is studded with projecting glycoproteins and surrounds a core consisting of matrix protein enclosed within which is a single strand of positive-sense RNA (Mr 6 × 106) associated with nucleoprotein. The envelope glycoproteins are responsible for attachment to the host cell and also carry the main antigenic epitopes, particularly the epitopes recognized by neutralizing antibodies[10].

## REPLICATION:

- After entering the cell, this virus sheds its capsid and releases its RNA genome into the cytoplasm. MERS-CoV has an RNA genome with a 5'-cap methylation and a polyadenine tail at the 3' end, and this allows its RNA molecule to bind to the ribosome for translation[11].
- The coronavirus also has a protein called RNA-dependent RNA polymerase (replica) encoded in its genome, which allows the viral genome to be transcribed and new copies produced using the host cell's machinery. RNA-dependent RNA polymerase is the first protein translated, and when the translation of this polymerase gene is finished, translation is stopped by the stop codon, this is known as interfering transcription[12].
- A non-structural protein, a protein that is encoded by the virus genome but is not structured and expressed in infected cells, is not present in RNA-dependent RNA polymerase enzymes[13].
- The RNA genome is transcribed and a long polyprotein is formed in which all the proteins are bound together. Corona virus has a non-structural protein - peptidase - that is able to separate proteins from each other in this translated chain. This method of transcribing viral proteins is a type of genetic economy of a virus that enables it to encode a large number of genes in a relatively small number of nucleotid.[14]

## CAUSATIVE DISEASES:

- Coronaviruses primarily infect the upper respiratory and gastrointestinal tracts in birds and mammals. It also causes a range of diseases in livestock and pets, some of which are dangerous and are considered a threat to the agricultural and animal husbandry activities.[15]

## VIRUS TRANSMISSION AND EPIDEMIOLOGY:

- It is believed that human-to-human transmission of coronaviruses occurs mainly between close people during direct contact through respiratory droplets from sneezing and coughing.[16]
- The novel coronavirus uses the same receptor as SARS-CoV [angiotensin-converting enzyme 2 (ACE2)] and mainly spreads through the respiratory tract. Human-to-human aerosol transmission is undoubtedly the main source of contagion, which happens mainly through contaminated droplets, hands or surfaces. Virus particles, which are present in secretions from an infected person's respiratory system, infect others through direct contact with mucous membranes [17]
- with a median incubation period of between 2 and 12 days (median 5.1 days) [18].
- An analysis of 22 studies revealed that human coronaviruses, including MERS-CoV and endemic human coronavirus, can persist on surfaces such as metal, glass or plastic for up to 9 days, but can also be efficiently inactivated within 1 min through a surface disinfection using 62–71% ethanol, 0.5% hydrogen peroxide or 0.1% sodium hypochlorite [19].
- Furthermore, most of the available evidence supports the thesis that social distancing of 1.5 m is enough to prevent airborne transmission.
- It appears that transmission is possible for approximately 8 days after symptoms appear. Patients may continue to show a positive pharyngeal swab for several weeks after remission of symptoms [20].
- however, viable virus cannot be detected after about 8 days of disease, suggesting that prolonged polymerase chain reaction (PCR) test positivity probably does not correlate with clinical transmission.
- Guidelines from the US Centers for Disease Control and Prevention do not precisely define the length of isolation for patients [21].
- It is reasonable to suggest that isolation is no longer necessary after two consecutive negative real-time (RT)-PCR tests at an interval of at least 24 h and in the absence of relevant clinical or epidemiological criteria.[22]
- General hygiene precautions are crucial in order to minimize the risk of contamination. Wearing masks, gowns, eye protection and gloves,especially for medical staff, are also recommended [23].

## PATHOGENESIS OF COVID-19:

- The pathogenic phases of COVID-19 remain incompletely understood. Previous studies have proposed SARS may consist of three phases: Viral replication, immune hyperactivity and pulmonary destruction.
- The clinical phases of COVID-19 have been recently proposed: Viremia phase, acute phase and recovery phase .
- It is generally hypothesized that the course of infection goes through the following stages: Viral invasion and replication, dysregulated immune response, multiple organ damage and recovery.
- Firstly, the virus enters the host cells, where it replicates, assembles and is released extracellularly to target cells, and this directly causes the damage and destruction of parenchymal cells such as alveolar epithelial cells. At the same time, a large number of pathogen associated molecular pattern (PAMP) and damage associated molecular pattern (DAMP) molecules are released to stimulate the innate immune response, induce inflammatory cell infiltration, release large quantities of cytokines, chemokines, proteases and free radicals, causing ARDS, sepsis and MODS.
- It has been observed that the pathological findings of COVID-19-induced pneumonia appear to resemble those seen in SARS-CoV-1 and MERS-CoV infection including bilateral acute changes with diffuse alveolar damage and vascular congestion, patchy inflammatory cellular infiltration, intra-alveolar edema, hemorrhage, proteinaceous exudate, denudation and reactive hyperplasia of pneumocytes, as well as the presence of multinucleated giant cells, but hyaline membrane formation was is not prominent observed.
- After the initial critical stage, the inflammatory response is gradually resolved, the damaged organ gradually recovers, and some of the damaged organs enter fibrosis and chronic stage, such as chronic critical illness, persistent inflammation, immunosuppression and catabolism syndrome.
- It is speculated that the major pathological alterations that take place in the vital organs during COVID-19 may be caused directly by the cytopathic effect mediated by SARS-CoV-2, and indirectly as a result of the harmful immune responses induced by SARS-CoV-2, but the relative importance of each of these requires further study. There is some evidence supporting the more important role of an abnormal immune response (rather than a direct viral cytopathic effect) in the effects of COVID-19. It has been observed that patients with COVID-19 had the highest viral load during the early stage .

- The timeline of COVID-19 infection showed that the median time from onset of symptoms to first hospital admission was 7 days, 9 days till ARDS, and 10.5 days till ICU .
- The association of worsening clinical progression with declining viral loads and the onset of an immunological response, plus the presence of significantly elevated cytokines levels suggested that severe lung damage was largely immunopathological in nature .[24]

## SYMPTOMS:

- COVID-19 affects different people in different ways. Most people who develop it have mild to moderate symptoms and recover without hospitalization.

✓ The most common symptoms:

1. Fever
2. Cough
3. Fatigue
4. Loss of sense of taste or smell
5. sore throat
6. headache
7. Aches and pains
8. Diarrhea
9. A rash or a change in the color of the fingers or toes
10. Eye redness or irritation Serious symptoms
11. Difficulty or shortness of breath
12. Loss of speech, movement, or confusion
13. pain in chest

✓ Older adu lts and people with several serious medical conditions are most likely to develop long-term symptoms of COVID-19, but even healthy young people may feel unwell for weeks or even months after infection[25].

## DIAGNOSIS

**-١Clinical diagnosis**

- The assessment of the patients with COVID-19 should be based on the clinical features and also epidemiological factors. The screening protocols must be prepared and followed per the native context. [26]
- The symptoms of COVID-19 remain very similar to those of the other respiratory epidemics in the past, which include SARS and MERS, but here the range of symptoms includes mild rhinitis to septic shock.[26]
- When examined, unilateral or bilateral involvement compatible with viral pneumonia is observed in the patients, and bilateral multiple lobular and sub-segmental consolidation areas were observed in patients hospitalised in the intensive care unit.[26]

2-Laboratory

- Collecting and testing of specimen samples from the suspected individual is considered to be one of the main principles for controlling and managing the outbreak of the disease in a country. The suspected cases must be screened thoroughly in order to detect the virus with the help of nucleic acid amplification tests such as reverse transcription polymerase chain reaction (RT-PCR).[26]
- It is also recommended that the suspected patients be tested for the other respiratory pathogens by performing the routine laboratory investigation per the local guidelines, mainly to differentiate from other viruses that include influenza virus, parainfluenza virus, adenovirus, respiratory syncytial virus, rhinovirus, human metapneumovirus and SARS coronavirus. It is advisable to distinguish COVID-19 from other pneumonias such as mycoplasma pneumonia, chlamydia pneumonia and bacterial pneumonia.[26]
- A Nasopharyngeal and oropharyngeal swab should be collected using Dacron or polyester flocked swabs. It should be transported to the laboratory at a temperature of 4°C and stored in the laboratory between 4 and −70°C on the basis of the number of days and, in order to increase the viral load, both nasopharyngeal and oropharyngeal swabs should be placed in the same tube. Bronchoalveolar lavage and nasopharyngeal aspirate should be collected in a sterile container and transported similarly to the laboratory by maintain a temperature of 4°C.[26]
- Several studies have shown that SARS-CoV-2 RNA can also be detected in blood and stool specimens [27].
- The gold standard method of confirming the suspected cases of COVID-19 is carried out by detecting the unique sequences of virus RNA through

reverse transcription polymerase chain reaction (RT-PCR) along with nucleic acid sequencing if needed. The various genes of virus identified so far include N, E, S (N: nucleocapsid protein, E: envelope protein gene, S: spike protein gene) and RdRP genes (RNA-dependent RNA polymerase gene).[27]

- Serological surveys are also considered to be one of the most effective ones in facilitating outbreak investigation and it also helps us to derive a retrospective assessment of the disease by estimating the attack rate.[27]
- According to the recent literature, paired serum samples can also help clinicians to diagnose COVID-19 in case of false negative results in NAAT essays.[27]
- The most common laboratory abnormalities reported on admission amongst hospitalized patients with pneumonia included leucopenia (9–25%) or leucocytosis (24–30%), lymphopenia (63%) and elevated levels of alanine aminotransferase and aspartate aminotransferase (37%) [27;28].
- Amongst 1099 COVID-19 patients, lymphocytopenia was present in 83%; in addition, 36% had thrombocytopenia and 34% had leucopenia [29].
- A mild thrombocytopenia, hypertransaminasaemia and an increase in lactate dehydrogenase have also been reported [30].
- Increased inflammation indices, usually including reduced procalcitonin and increased C-reactive protein (CRP) levels, are associated with clinical severity. Young et al. observed an average CRP level of 1.1 mg/dL in patients with normal percentage oxygen saturation (SatO2) and of 6.6 mg/dL in hypoxaemic patients [28].
- Moreover, Ruan et al. observed a correlation between CRP and mortality risk [31].
- • Increased troponin was also reported in 7% of patients who subsequently died because of fulminant myocarditis [32].
- Troponin appears to be a strong prognostic indicator of mortality. Finally, it was noticed that D-dimer and ferritin levels were usually high in hospitalized patients.[32].

2- Radiology

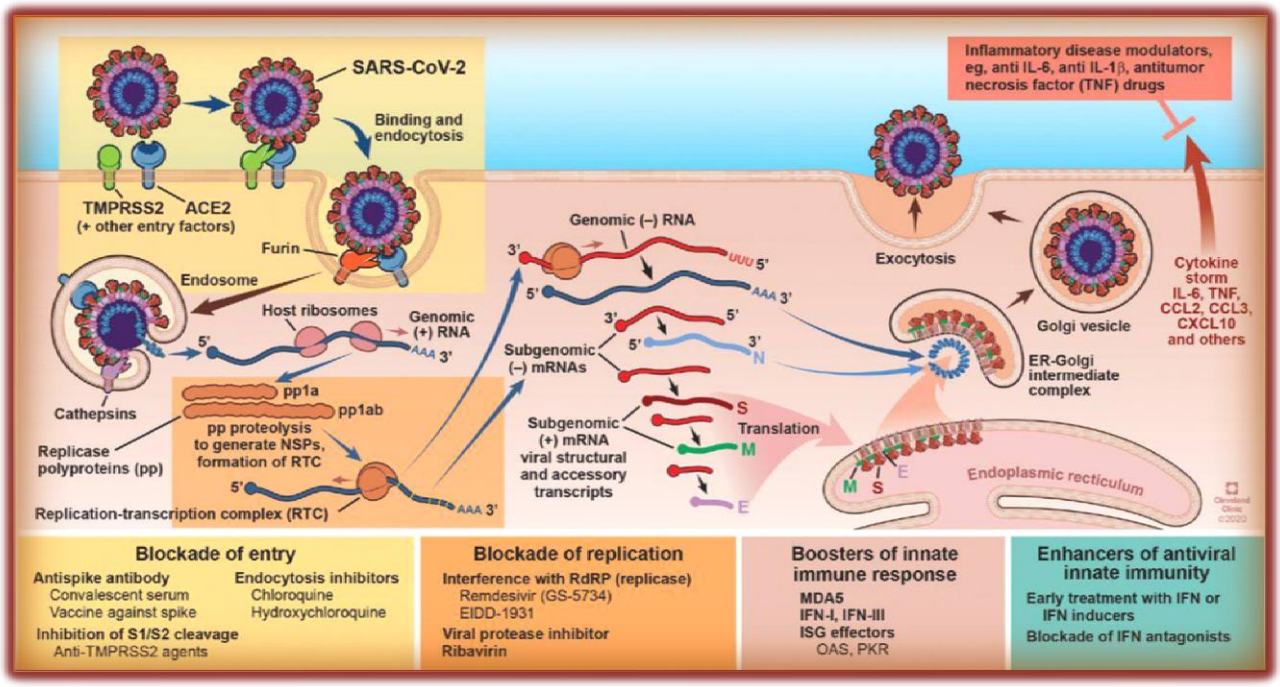
- Typical CT findings in individuals with COVID-19 were ground-glass opacities, particularly on the peripheral and lower lobes, and bilateral multiple lobular and subsegmental areas of consolidation, especially in ICU patients [17].
- The number of lung segments involved was found to be related to disease severity. These opacities tended to flow together and thicken with progression of the disease. [33]

## TREATMENTS:

- Scientists around the world are working to find and develop treatments for the COVID-19 virus. Currently, there are no registered drugs to treat COVID-19 disease [34]
- and management is based mainly on supportive therapy and on treating the symptoms and trying to prevent respiratory failure. Most of the data available for pharmacological treatments derive from medications used during the SARS-CoV or MERS-CoV pandemics or from in vitro observations [35,36].
- Several clinical trials of possible treatments for COVID-19 are underway, based on antiviral, anti-inflammatory and immunomodulatory drugs, cell therapy, antioxidants and other therapies. The most step and drugs that aid in manegment of thre patients:
- Optimal supportive care includes the supply of oxygen for severely ill patients and those at risk of severe injury, along with more advanced respiratory support such as ventilators for critically ill patients. Oxygen therapy will be required if hypoxia is present (SatO2 < 93%) or if symptoms of respiratory distress become evident. Oxygen therapy is generally administered through a (high-flow) nasal cannula, a face mask or noninvasive ventilation [37,38].
- Arterial SatO2 must be monitored constantly during oxygen therapy.
- If a sufficiently high arterial O2 level (SatO2 93–96%) is not reached, and if acute lung injury develops (ratio of arterial partial pressure of oxygen to fractional inspired oxygen ≤ 200 mmHg), invasive mechanical ventilation and intubation are required [19].
- 2-Dexamethasone is a corticosteroid that can help shorten the length of time a patient stays on a ventilator and save the lives of critically ill patients.[39]
- 3-Anticoagulation therapy is recommended in patients with early-stage COVID-19, especially when the D-dimer value is 4 times higher than normal. Infection, inflammation and other disease-related factors can cause overactivation of coagulation, increasing the risk of augmented ischaemic events and disseminated intravascular coagulation [39].
- 4- Antiviral drugs: Remdesivir was successfully used in several COVID-19 patients in China [40]

- As a nucleotide analogue, remdesivir acts through incorporation into the nascent viral RNA chain and subsequently causes its premature termination. Remdesivir has been reported to be active in preclinical studies of SARS-CoV and MERS-CoV infections by acting on the viral polymerase of coronaviruses [41].
- A North American study of MERS-CoV in mice has shown the effectiveness of remdesivir in reducing viral load and improving lung function parameters [42].
- Clinical efficacy trials of the use of remdesivir in COVID-19 patients are currently underway, both in China and the USA.
- The second-generation antiretroviral drug combination lopinavir/ritonavir inhibits viral protease. The combination is widely available and drug interaction and safety profiles are well established. The efficacy of lopinavir/ritonavir against SARS-CoV has been demonstrated [56], and these drugs also seem to reduce the viral load in COVID-19 patients [43,44].
- 5-Chloroquine and hydroxychloroquine are used for the treatment of malaria and amoebiasis. They both show a good tolerability profile. Various studies have demonstrated chloroquine activity in vitro and in animal models against SARS-CoV [61;62]and avian influenza [45].
- Their antiviral efficacy seems to be explained by an increase in endosomal pH which is necessary for fusion between the virus and the host cell; they also seem to interfere with the ACE2 cell receptor and have immunomodulatory activity. We have also found evidence of their efficacy in COVID-19 patients [46,47].
- In vitro, hydroxychloroquine is more potent than chloroquine in inhibiting SARS-CoV-2 [17].
- Data on the efficacy of chloroquine and hydroxychloroquine remain inconclusive, and further studies are warranted. Several issues need to be clarified such as the stage of COVID-19 disease at which these medications could provide the best therapeutic benefit, or whether they may play a role in disease prophylaxis for high-risk patients and healthcare providers [48].
- Finally, it seems that antimalarial medications may act synergistically with macrolides (e.g. azithromycin) for enhanced antiviral effect but, once again, the existing evidence is limited [49] and studies had several limitations (e.g.

lack of randomization and covariate-adjusted analysis, and potential selection bias).



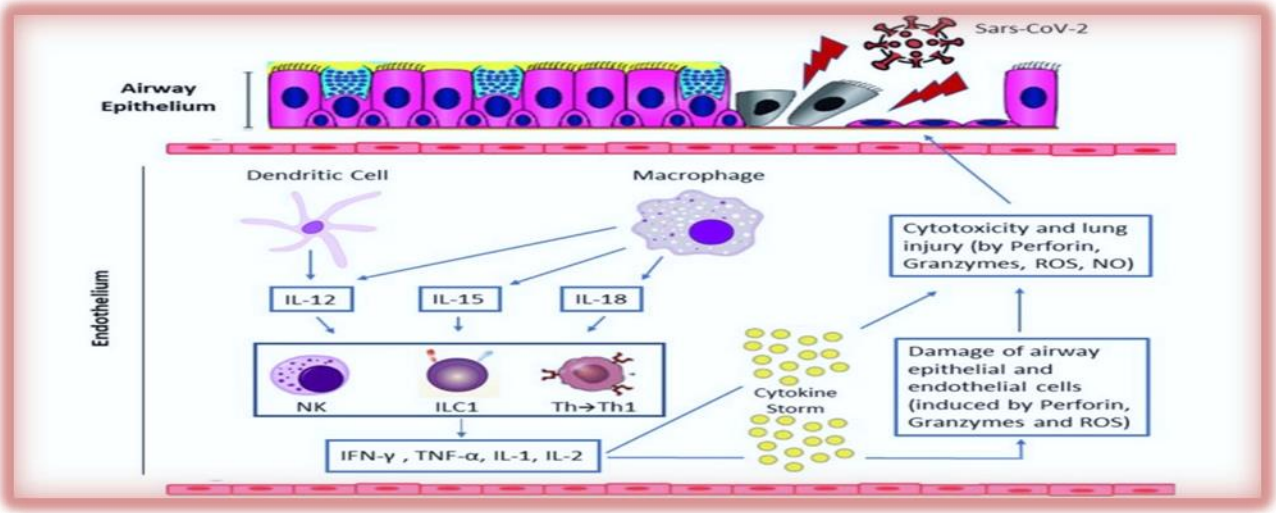

- Finially, It is fundamental to ensure patient isolation in order to avoid transmission to other patients, family members and healthcare providers. Quarantine measures must be taken to isolate infected individuals, both symptomatic and asymptomatic, and anyone who may have been in contact with them [50.
- Entire populations must limit social contact and minimize the time spent outside [51].
- In mild cases, self-isolation at home is the best option, whilst maintaining adequate hydration and nutrition and treating symptoms such as fever, sore throat or cough. Thus, hospital beds can be available for severe cases [52].

## IMMUNE RESPONSE TO VIRUS

Virus-induced inflammation pathway. Immune cells are sequentially activated to limit virus dissemination. Dendritic cells and macrophages act as first-line antigen-presenting cells which, following virus antigen recognition, produce cytokines, including interleukin (IL)-12, IL-15 and IL-18.

Their interaction determines the chemotaxis and activation of natural killer (NK) cells, the recruitment of Group 1 innate lymphoid cells (ILC1) and the differentiation of T helper (Th) lymphocytes into Type 1 helper (Th1) cells. The latter are associated with an increased expression of cytokines, including interferon (IFN)-γ, tumour necrosis factor (TNF)-α, IL-1 and IL-2, with consequent activation of NK cells, secreting perforin, granzymes, reactive oxygen species (ROS), nitric oxide (NO) and cytotoxic T lymphocytes in order to kill the virus.

Excess neutrophils and persistently activated macrophages cause extensive damage to the lung epithelium and endothelium, resulting in an alveolar capillary barrier. The disruption of this barrier allows protein-rich fluid to enter the alveoli, causing fluid accumulation in alveolar spaces (noncardiogenic pulmonary oedema) which interferes with gas exchange.[53,54,55]




## CORONAVIRUS VACCINES:

- Vaccine development has been ongoing since the beginning of 2020, and everyone is hoping that the vaccines can help stop the spread of disease[56].
- While the coronavirus vaccines have been widely distributed, there are still more than 90 million Americans who remain unvaccinated[57].
- It is important that people know the truth about the vaccines so they can make an educated decision on being vaccinated[82]. There are many types of coronavaccine, but most commone types that vaccinated by the people are:

  a) Pfizer/BioNTech(mRNA COVID-19 vaccines)

  b) Moderna(mRNA COVID-19 vaccines)

  c) AstraZeneca (a viral vector vaccine)

d) Johnson & Johnson - Janssen Pharmaceutical(a viral vector vaccine)

- ✓ vaccines that are approved or authorized for use in the United States or that are undergoing large-scale (Phase 3) clinical trials in the United States.[58]

## HOW COVID-19 VACCINES WORK:

- COVID-19 vaccines help our bodies develop immunity to the virus that causes COVID-19 without us having to get the illness.
- Different types of vaccines work in different ways to offer protection. But with all types of vaccines, the body is left with a supply of "memory" T-lymphocytes as well as B-lymphocytes that will remember how to fight that virus in the future.[59]
- It typically takes a few weeks after vaccination for the body to produce T-lymphocytes and B-lymphocytes. Therefore, it is possible that a person could be infected with the virus that causes COVID-19 just before or just after vaccination and then get sick because the vaccine did not have enough time to provide protection.[60]
- Sometimes after vaccination, the process of building immunity can cause symptoms, such as fever. These symptoms are normal and are signs that the body is building immunity[61].

## CONCLUSION:

- The COVID-19 pandemic has had devastating effects on people's lives all over the world – with many hundreds of thousands of people dying with the virus and widespread collateral damage of attempts to control the spread and reduce the health impacts of the virus. It has also presented the scientific community with some difficult challenges – many of them still to be addressed.
- As the results of the studies analyzed more than two years after the outbreak of the pandemic show, there are many "recoveries" that may not have fully recovered as hoped
- When we wrote this research, our ability to provide a definitive conclusion may have been negatively affected by some limitations, such as low sample size, differently applied methods, dissimilar reference ranges, asynchronous representation of results, and diversity of patients. . Despite limitations, analysis of the current scientific results obtained demonstrates the value of

laboratory tests as simple, rapid, and cost-effective biomarkers in COVID-19 patients.

- Specifically designed randomized clinical trials are urgently needed to determine the most appropriate evidence-based treatment modality to reduce the spread of this disease and prevent the burden of any future outbreak.

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