زانکۆی سەلاحەدین - هەولێر
Salahaddin University-Erbil

Evaluation of the level of (CRP, Ferritin and vitamin D_3) in the blood serum of patients infected with COVID-19

Reseach Project

Submitted to the department of (chemistry) in partial fulfillment of the requirments for the degree of BSc. In (chemistry)

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Supervisor recommendation

I am the student's supervisor , **Rayan Hamid Ismail** . I Support that the student has completed all the requirements for submitting the research drawn entitled **(Evaluation of the level of(CRP, Ferritin and vitamin D_3) in the blood serum of patients infected with COVID-19)** according to the numbered admininistrative order 31/5/1972 on 9th oct.2022 in accordance with the instruction of Salahaddin university quality assurance and it is ready for discussion.

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Rayan Hamid Ismail

Abstract

Coronavirus disease (COVID-19) is defined as illness caused by coronavirus called severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) and appeared in Wuhan, China, in December 2019.The biochemical variables or parameters were determination and evaluation including (CRP, Ferritin and VitaminD_3). First, vitamin D_3 was projected to increase 25-hydroxyvitamin D levels and shorten hospital stays because it acts as hormones in the body rather than a vitamin and patients with inadequate immune systems. According to studies, those who were infected with the evolving coronavirus had much greater levels of CRP in their blood serum than those who were in good condition. Although ferritin is frequently used to indicate the whole body iron reserves, its predictive value is associated with COVID-19. The purpose of this study was to evaluate the relationship between ferritin and severity in hospitalized patients with coronavirus disease 2019 (COVID-19) and to explore the idea that ferritin functions as an independent predicator of mortality. That is why the infected patients have high levels of ferritin.

Keywords: Virus, COVID-19, VitaminD_3, Ferritin and CRP.

CONTENT

LIST OF FIGURE

LIST OF ABBREVIATIONS

Symbol	*Description*
CRP	C-reactive protein
TMV	Tobacco mosaic virus
DNA	Deoxyribonucleic acid
RNA	Ribonucleic acid
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HSV-1	Herpes simplex virus type 1
HIV	Human immunodeficiency virus
MLV	Murine leukemia virus
SINV	Sindbis virus
NPC	Nuclear pore complex
MERS-COV	Middle east respiratory syndrome coronavirus
ARDS	Acute respiratory distress syndrome
VACV	Vaccine virus
MHC	Major histocompatibility complex
SARS-COV	Severe acute respiratory syndrome coronavirus
UV	Ultra violet
LDH	Lactate dehydrogenase
WHO	World health organization
COVID-19	Coronavirus disease 2019
PM	Particulate matter
TNF	Tumor necrosis factor
IU	International units
ICU	Intensive care units
HSPG	Heparan sulfate proteoglycan

1-Introduction

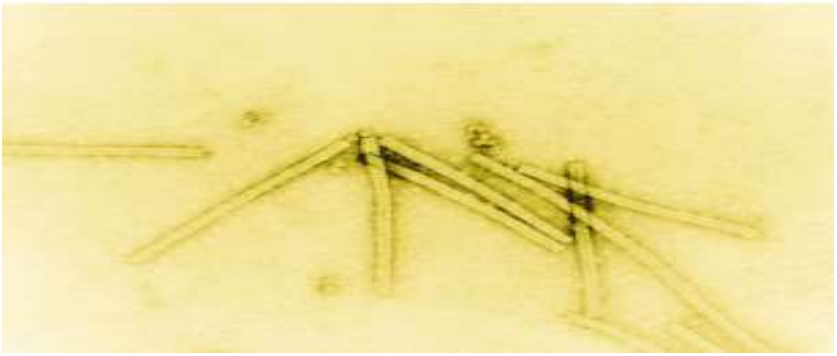
In the past, viruses were described as tiny infectious agents that could slip through filters that could capture even the tiniest cells. The classification of viruses as intracellular parasites that are obligate dependent on their cellular hosts for energy and chemical building blocks led to this development. These characteristics, however, are not enough to clearly identify viruses as they are now believed to be. Discussing various methods for defining viruses, examine the limits of the virosphere within the virtual world of replicators, and analyze the interactions between viruses and different kinds of replicators. Viruses, whatever they may be defined, have undoubtedly evolved from nonviral replicators like plasmids on numerous occasions by enlisting host proteins to serve as components of virion. On the other hand, different varieties of replicators have repeatedly arisen from viruses. As a result, the virosphere is a dynamic system with substantial evolutionary traffic flowing through its limits (Koonin, Dolja et al. 2021).

A new field is virology. Since viruses were first identified as disease-causing agents, a little more than 100 years have passed. It was the late 19th century, and tobacco, a plant from the New World that had been brought to Europe as part of the Columbian Exchange, was widely consumed there. (Zerbini and Kitajima 2022)

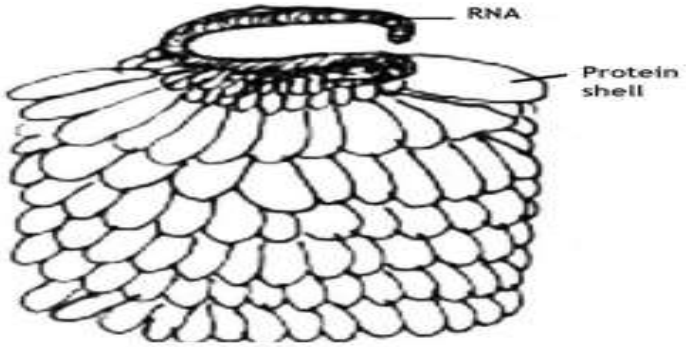
Since the late 14th century, harmful chemicals have been referred to as "viruses" (from the Latin term virus, which means "slimy liquid" or "poison"). The agents that cause venereal disease (today's specific bacteria), as well as subsequently, all infectious agents, were referred to as "viruses" without distinction as early as 1728. In 1892, Ivanovskij showed that the sap of a sick tobacco plant retained its infectious properties even after passing through Pasteur-Chamberland filters (average hole size: 0.2 mm), which were employed to keep cellular organisms like bacteria at bay. Beijerinck made similar observations shortly after, noting that filtered diluted tobacco plant sap was just as contagious as undiluted sap. Contagium vivum fluidum was Beijerinck's term for the substance found in the filtered sap (a contagious living liquid). As a result, infectious agents that could pass through Pasteur-Chamberland filters were referred to as "ultra (filterable) viruses," and the pathogen responsible for tobacco mosaic disease was given the name tobacco mosaic virus (TMV). As it became increasingly clear that some agents selectively infected specific cellular organisms, the term "virus" was chosen to refer only to nonorganismal/noncellular filterable agents. As a result, the term "virus" came to be mainly defined by what it was not, namely, that viruses were noncellular, sub-light-microscopic infectious agents that could be filtered out of other infectious agents. (Koonin, Dolja et al. 2021)

1.1- Virus as particle

There was a general belief that a virus must be some sort of microscopic thing as scientists learned more and more about diseases caused by viruses in humans, animals, plants, and microorganisms. How might a "mere" fluid be able to reproduce? Wendell Stanley, an American scientist, was able to create crystals from the juice of plants affected by tobacco mosaic disease in 1935 via a complex chemical procedure. The crystals' potential to cause tobacco mosaic disease was preserved in highly diluted solutions prepared from them. He thought the crystals were protein, and soon discovered that the viruses were made of both protein and nucleic acids (DNA or RNA). It took some time for researchers to "see"—in this case, to produce an image of—virus particles thanks to the development of the electron microscope, which offered far greater magnification than light microscopes. (Holdrege 2020)



With the use of a heavy metal, a virus's structural details were made apparent in this image of a tobacco mosaic virion (a virus particle), which was then enlarged by a factor of 160,000 using an electron microscope (public domain image).



Detail of a rod-shaped tobacco mosaic virion's intricate structure as seen in a diagram. The coiled RNA core is by the coiling protein covering (public domain image).

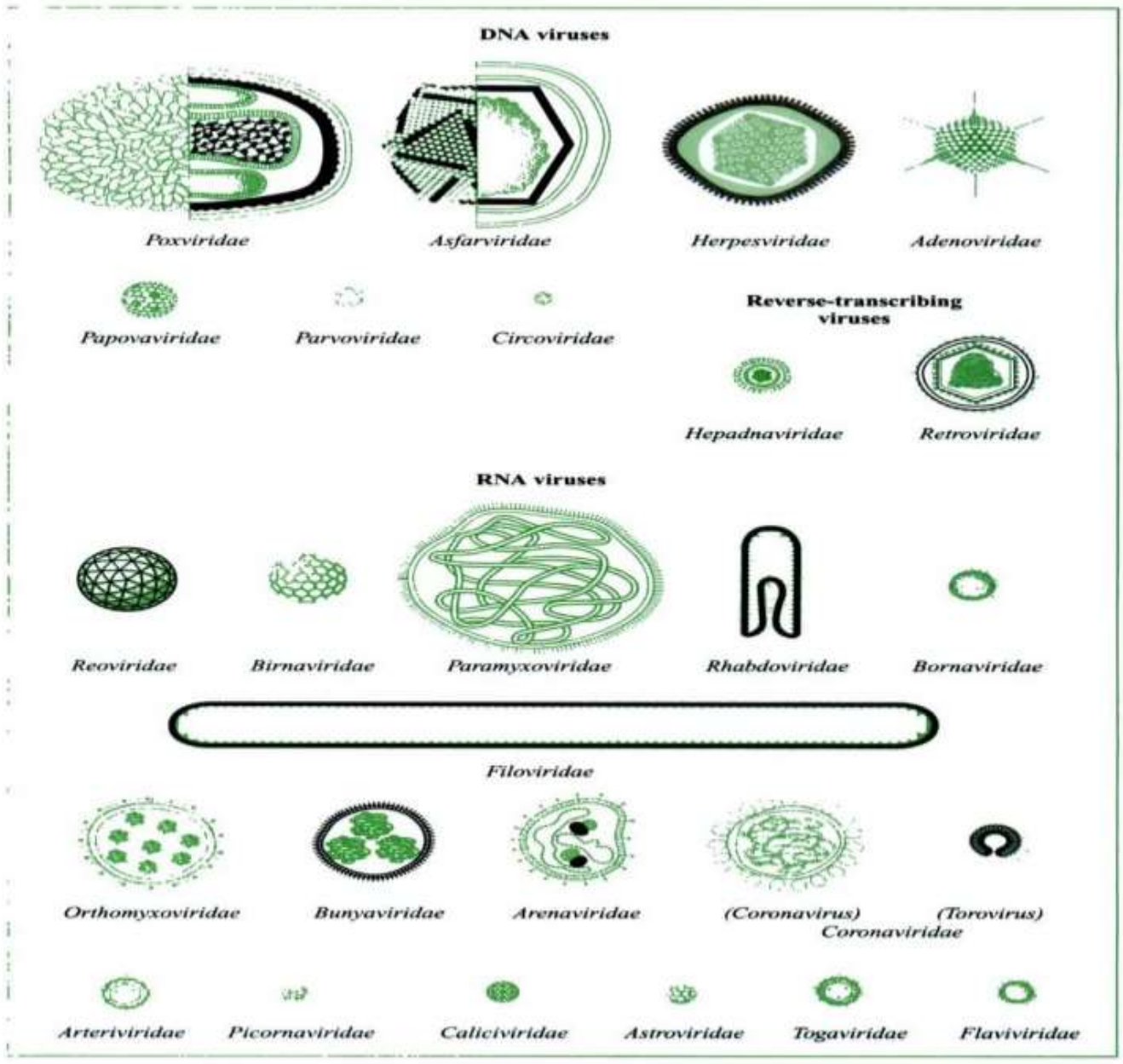


Fig.1 depicts the general sizes and forms of many virus families.

The function and formation of virus particles role of viral particles and how they are created Since so much information concerning virus anatomy is highly visual in nature, it is challenging to accurately convey it in literature. It is highly advised that the reader view the virus structure resource. **Fig.1** also depicts the approximate sizes and forms of many virus families..(Cann 2001)

Table 1
Summary of representative viruses and their cell binding receptors, ligands, and other properties.

Name of viruses	Virus type & genome type	Cell surface receptor and tissue/cell tropism	Viral ligands for tropism	Therapeutic agents delivered
Cytoplasmic virus (delivery and replication in cytoplasm)				
SINV	Enveloped ssRNA (+)	Heparan sulfate; Tropism unknown	Viral E glycoprotein	miRNA
WNV	Enveloped ssRNA (+)	Tropism: epithelial cells in the skin, kidney, intestine and testes	Viral envelope protein E	miRNA
Vesiculovirus	Enveloped ssRNA (−)	Tropism: mainly neurons	Viral G glycoproteins	shRNA, miRNA
DENV	Enveloped ssRNA(+)	Sulfated glycosaminoglycans (GAGs), lectins that recognize carbohydrates, glycosphingolipid (GSL) Tropism: Monocytes/macrophages, phagocytes, hepatocytes	Viral envelope protein E	NA
Ebola virus	Enveloped ssRNA(−)	Niemann–Pick C1 (NPC1), a cholesterol transporter protein; TIM-1 (aka HAVCR1) Tropism: Liver, skin, spleen, lymph nodes and gastrointestinal tract; fibroblasts	Glycoprotein, phosphatidyl serine	NA
HCV	Enveloped ssRNA(+)	CD81, SR-BI, claudin-1 (CLDN1), Heparan sulfate, LDL-R	Viral envelope protein E	NA
Rabies virus	Enveloped ssRNA(−)	Nicotinic acetylcholine receptor (nAChR), the neuronal cell adhesion molecule (NCAM), and the p75 neurotrophin receptor (p75NTR) Tropism: Primarily neuronal tissue	Viral G glycoproteins	NA
VACV	Enveloped dsDNA	Heparan sulfate Tropism: Dendritic cells, monocytes/macrophages, B lymphocytes, primary hematolymphoid cells	Surface (SU) and transmembrane (TM) glycoproteins	NA
Nuclear virus (delivery and replication in nucleus)				
AdV	Non-enveloped dsDNA	CAR, CD46, sialic acid, CD80/86, heparan sulfate, $\alpha_v\beta_3$- and $\alpha_v\beta_5$-integrins Tropism: Epithelial cells and lymphoid cells	Viral fiber glycoproteins	DNA, siRNA, shRN
AAV	Non-enveloped ssDNA	HSPG, Human fibroblast growth factor receptor 1, $\alpha_v\beta_5$ integrin		DNA, siRNA, shRNA, miRNA
SV40	Non-enveloped dsDNA	MHC class I molecules		NA
CMV	Enveloped dsDNA	Epidermal growth factor receptor, heparan sulfate	Envelope glycoproteins	NA
HBV	Enveloped dsDNA(RT)	NTCP, HSPG Tropism: Hepatocytes	Major surface antigen	NA
HSV-1	Enveloped dsDNA	HSPG and glycoprotein Tropism: Epithelial cells and neutrons		DNA, miRNA
HIV	Enveloped ssRNA(RT)	CD4, chemokine receptors, glycosphingolipids Tropism: T cells, dendritic cells or macrophages, brain cells	Glycoprotein (gp120, gp41)	DNA, siRNA, shRNA, miRNA
SIV	Enveloped ssRNA(RT)	CD4, CXCR4, CCR5		shRNA
Influenza A virus	Enveloped ssRNA(−)	Sialic acids Tropism: Respiratory tract	Hemmaglutinin (HA) protein	RNA, miRNA

Adeno-associated viruses Adenovirus, Cytomegalovirus, Dengue Virus HBV: Hepatitis B virus, HCV: Hepatitis C virus, HSV-1: Herpes simplex virus type 1, HIV: Human immunodeficiency virus, MLV: Murine leukemia viruses Sindbis virus, SINV SIV stands for Simian Immunodeficiency Virus, SV40 for Simian Vacuolating Virus 40, and WNV for West Nile virus, and VACV for vaccine virus. GAG stands for glycosaminoglycans, CAR for coxsackie and adenovirus receptor, and MHC for major histocompatibility complex. Dystroglycan 1 (DAG1), CCR5 (C-C chemokine receptor type 5), CXCR4 (C-X-C motif) receptor 4, heparan sulfate proteoglycan (HSPG), and XPR1 (xenotropic and polytropic retrovirus receptor) are examples of glycan.(Ni, Zhou et al. 2016)

Model of virus

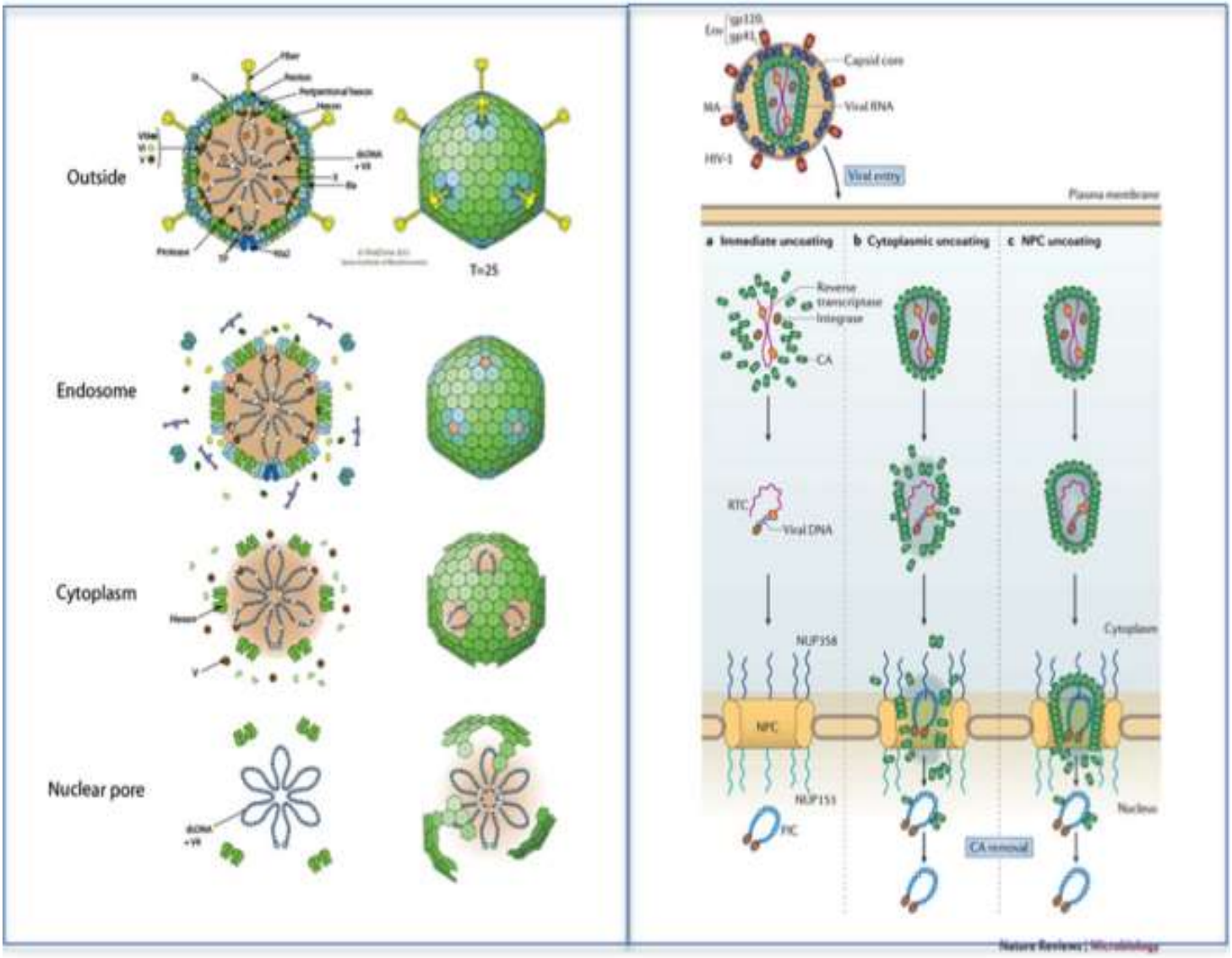


***Fig.2* Model for virus breakdown**. (A) Viral disassembly during intracellular trafficking, using the human adenovirus type C virion as an example. Models for the removal of the nucleocapsid core of HIV-1 Immediate uncoating occurs shortly after HIV-1 fuses with the plasma membrane and is swift. Cytoplasmic uncoating occurs after partial disassembly in the cytoplasm, with some remaining bound to the genome until nuclear entry. NPC uncoating occurs after the core is intact in the cytoplasm and begins to uncoat at the nuclear pore complex (NPC) Published with permission from Nature Publishing Group and ViralZone.(Ni, Zhou et al. 2016)

1.2-Covid-19 virus

Since December 2019, the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2)-caused coronavirus disease 2019 (COVID-19) has swiftly grown into a global outbreak that is defined by a human-to-human transmission. WHO declared the COVID-19 pandemic on March 11, 2020. As of September 20, 2020, it had resulted in 30 675 675 verified cases, including 954 417 fatalities. 3 Patients who have comorbid conditions like diabetes, heart disease, underlying respiratory disorders, and cancer are at a higher risk of developing serious consequences and even passing away. The fight against this global calamity will require the combined efforts of all humankind. Inflammatory cytokines like TNF- α, IL-6, IL-12, and IL-8 are released in large quantities during the progression of the disease, potentially leading to acute respiratory distress syndrome (ARDS) and systemic organ failure. The cytokine storm is an uncontrolled and dysfunctional immune response in the immunopathogenic mechanism of COVID-19 similar to the one in severe influenza. According to evidence, the levels of serum ferritin, d-dimer, lactate dehydrogenase, and IL-6 rise as the condition worsens, indicating a higher chance of death. (Cheng, Li et al. 2020)

Corona virus was first discovered as a cold in 1960. Up until 2002, corona was considered a simple, non-lethal virus. Numerous studies detailing the spread of the corona to numerous nations, including the United States, Taiwan, Hong Kong, Singapore, Thailand, and Vietnam, were published in 2003. More than 1000 patients died from severe acute respiratory syndrome brought on by corona in 2003, according to reports. The year was terrible for microbiologists. Microbiologists initially concentrated on comprehending these issues. After a thorough exercise, they draw a conclusion, comprehend the mechanism of disease, and identify the corona virus. However, 8096 patients in all have had corona virus infection verified to date. Therefore, a "state emergency" was proclaimed in 2004 by the World Health Organization and the Centers for Disease Control and Prevention. In a different study from Hong Kong, 50 patients with severe acute respiratory syndrome and 30 of them with corona virus infection were confirmed. A number of infected patients and deaths were reported in Saudi Arabia in 2012. (Kumar, Malviya et al. 2020)

In Wuhan, China, a novel coronavirus (COVID-19) pneumonia first appeared in December 2019. Since then, the deadly COVID-19 virus has been spreading over the world and killing an increasing number of people. Fever, exhaustion, a dry cough, and dyspnea are the symptoms of novel COVID-19-infected pneumonia (NCIP). There have been several chest imaging characteristics reported that are comparable to those in other coronavirus disorders.(Kooraki, Hosseiny et al. 2020).

The severe acute respiratory syndrome coronavirus (SARS-CoV), Middle East respiratory syndrome, and other novel coronaviruses have brought forth COVID-19, a new viral disease that has gripped the entire world (MERS-CoV). SARS COV-2, which seems to be the only one with a chance of spreading globally.

End of December 2019 saw the COVID-19 case reported in Wuhan, which is in the Hubei region of Central China. It is believed that the sea food market played a role in this epidemic, which was quickly shut down.On January 30, 2020, the World Health Organization subsequently declared a Public Health Emergency of International Concern. SARS and MERS corona viruses both have bats as their reservoirs, and camels and palm civets, respectively, were the sources of human infection. This virus can spread via droplets in the air. There is no known natural reservoir or intermediate host for COVID-19. (Chathappady House, Palissery et al. 2021)

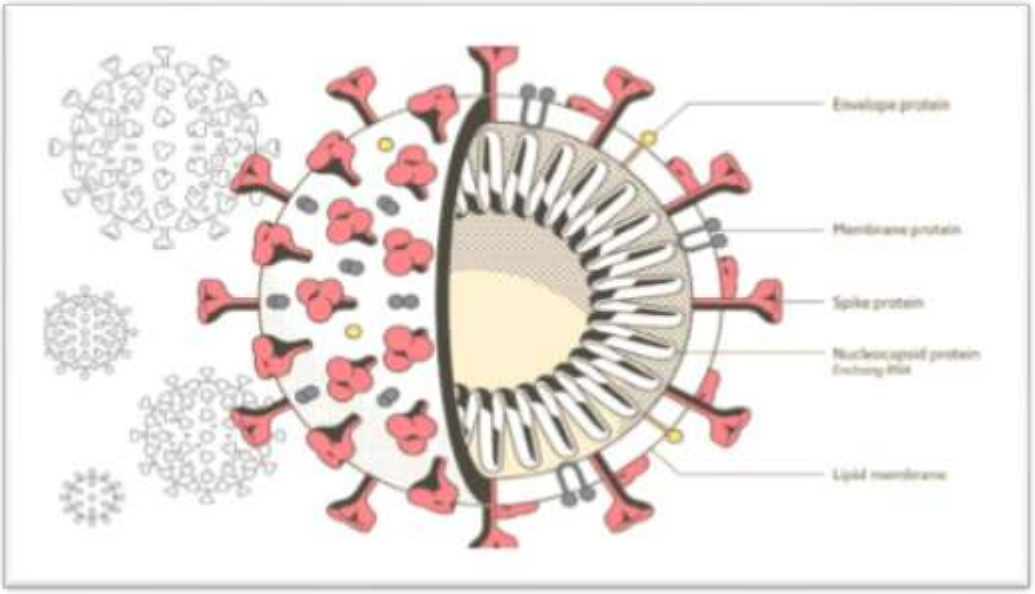


Fig .3 structure of covid-19

The structure of COVID-19 is shown in Fig.3 they are made up of the nucleocapsid, where the genetic material is strictly contained (exclusively a simple ribonucleic acid (RNA) sequence of about 32,000 bases), and packaged thanks to protein N, and the envelope, which is made up of various structural proteins like the membrane glycoprotein or M protein, involved in virus assembly and in contact with the nucleocapsid, protein S, which forms the spikes responsible for adhesion to the host cell, and protein E, which inter These are the most important structural proteins, and it can be shown that the genomic sequence of COVID-19 is considerably different from that of MERS-CoV (50%) and fairly similar to that of SARS-CoV (79%) .(Al-Zubaidi and Mijwil 2021)

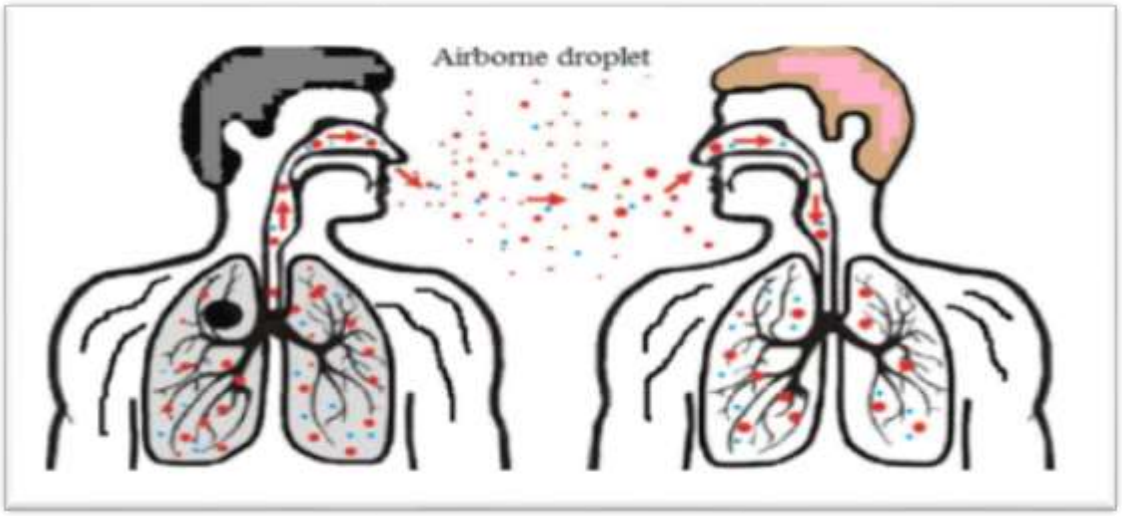


Fig. 4 Transission of corona virus via airborne droplets

This figure quantity It is thought that bacteria in airborne particulate matters (PM) or dust are associated to infectious diseases produced by coughing, sneezing, kissing, and smooching. The corona virus was spreading from person to person via close contact via aerosol droplets. The COVID-19 virus may be transported over great distances by adhering to airborne dust and particulate matter (PM). So, refrain from engaging in these activities with partners or family members who are sick . (Qu, Li et al. 2020)

2- Parameters

2.1- Vitamin D_3

When exposed to ultraviolet light, the skin of humans produces vitamin D_3 (cholecalciferol) from 7-dehydrocholesterol. The active form of vitamin D, 1α, 25-dihydroxyvitamin D_3 [1, 25 $(OH)_2$ D_3], is involved in the metabolism of calcium and phosphate and has numerous other biological functions. Although promoting insulin secretion, innate immunity, and cellular differentiation, vitamin D_3 suppresses the production of parathyroid hormone, adaptive immunity, and cell proliferation. The concept of vitamin D_3 having a dual function as an essential organic substance that has been shown to have a crucial impact on immune responses as well as an important sec steroid hormone for the regulation of body calcium homeostasis has been inspired by the role of vitamin D_3 in immune regulation. Several observational studies have found a link between low vitamin D_3 levels and increased risk of inflammatory and immune-mediated illnesses. The two main forms of in people, vitamin D_3 (cholecalciferol), are produced in the skin when UV radiation is exposed to 7-dehydrocholesterol (Sakaki, Kagawa et al. 2005).

One of vitamin D's active metabolites, 1α, 25-dihydroxyvitamin D_3 [1, 25$(OH)_2$ D_3], plays a significant role in the metabolism of calcium and phosphate and has a variety of other biological effects. Insulin secretion, innate

immunity, and cellular differentiation are all stimulated while parathyroid hormone secretion, adaptive immunity, and cell proliferation are all inhibited by vitamin D_3.

A increased susceptibility to immune-mediated illnesses and inflammatory diseases has been linked by recent observational studies with altered vitamin D_3 levels. Vitamin D_2 (also known as ergocalciferol) and vitamin D_3 [$1,25(OH)_2D_3$], commonly referred to as cholecalciferol or calcitriol, are the two main forms of vitamin D. Unlike $1,25(OH)_2D_3$, which is generated in relatively significant amounts by humans and the majority of vertebrate animals, vitamin D_2 is formed by plants and fungi but is not produced in vertebrates. The primary source of $1,25(OH)_2D_3$ is photosynthesis, which takes place in the skin. UV light catalyzes the first step in $1,25(OH)_2D_3$ biosynthesis, which transforms 7-dehydroxycholesterol into pre-vitamin D_3. This is followed by a spontaneous and temperature-dependent isomerization that results in $1,25(OH)_2D_3$ synthesis. Vitamin D_3 must first be converted in the liver to 25-hydroxyvitamin D_3 [$25(OH)D_3$]$_6$ at the carbon 25-position by 25-hydroxylase in order to produce the physiologically active form . (Di Rosa, Malaguarnera et al. 2011)

Fig.5 Two stages of hydroxylation are performed on vitamin D_3. $25(OH)D_3$ is created as the initial step in the liver at position 25. The most powerful form of vitamin D_3, 1α ,$25(OH)_2D_3$, is created in the second phase at the 1α location in the kidney. Through encouraging intestinal absorption of calcium and phosphorus, kidney reabsorption of phosphate, and release of calcium and phosphate, this active form of vitamin D_3 plays a crucial role in calcium homeostasis.(Sakaki, Kagawa et al. 2005)

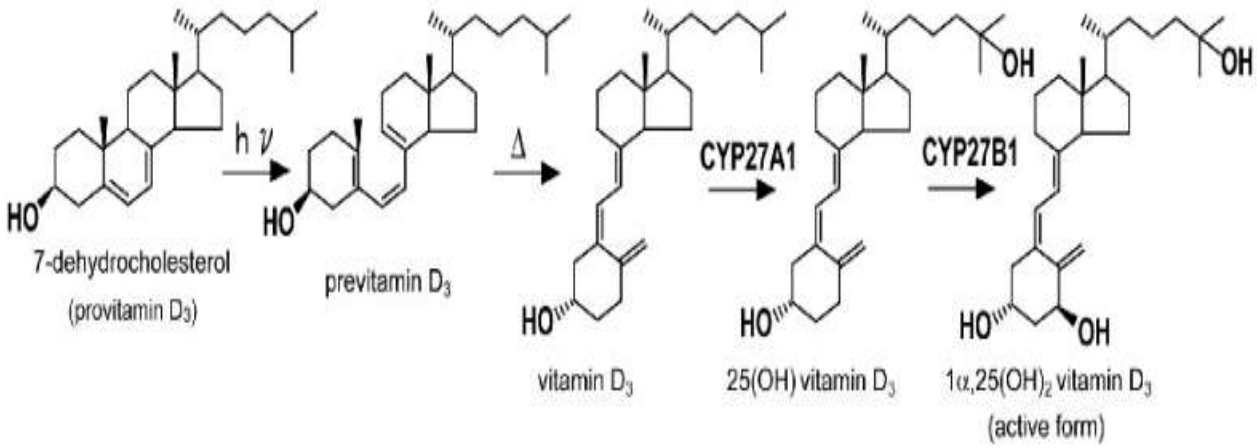


Fig. 5 Synthetic pathway of active form of vitamin D_3. The schematic pathway of vitamin D_3 shows the conversion of 7- dehydrocholesterol to an active form of vitamin D_3 ($1α,25(OH)_2D_3$) by the action of light exposure (hν) in the skin, heatinduced isomerization (Δ) , CYP27A1 in the liver, and CYP27B1 in the kidney.

2.2- C-reactive protein (CRP)

CRP is a pentameric plasma protein that takes part in the body's overall inflammatory response. It has homologs in both vertebrates and a wide variety of invertebrates. It is a pattern recognition molecule that is highly sensitive and non-specific for the acute phase of inflammation . The liver creates the protein CRP, When there is inflammation in the patient's body, the liver releases more CRP into the bloodstream despite having low levels of CRP in the patient's bloodstream normally. The c-reactive protein test quantifies the amount of CRP present in a sample of human blood. A significant medical illness that produces inflammation and high levels of CRP may be present.Physiological effects of CRP In the development of cardiovascular disease, C-reactive protein (CRP) plays a role. It is a cardiovascular disease marker and predictor. Many cardiovascular effects of CRP, including clotting, oxygen radical production, an increase in the expression of adhesion molecules and plasminogen activator inhibitor-1, and plaque destabilization, may contribute to cardiovascular disease. (Prasad 2006)

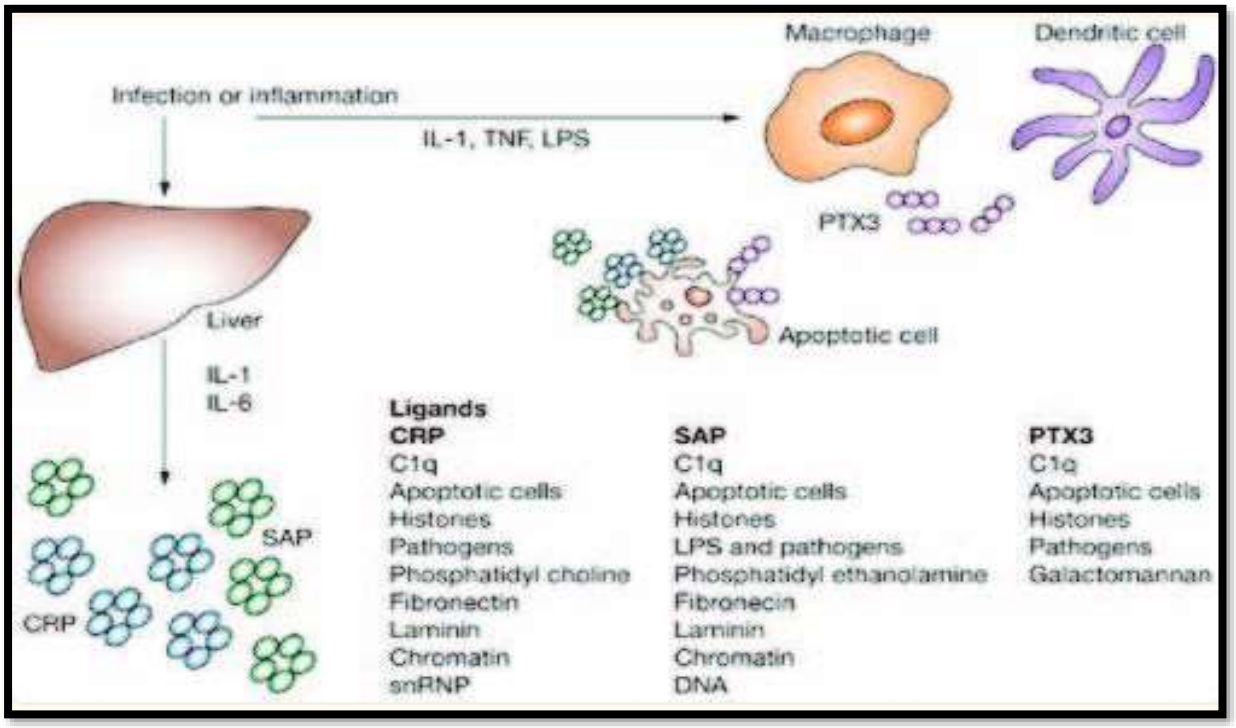


Fig. 6 Synthesis of C-reactive protein

Fig.6 synthesis of CRP It is also produced in response to many different types of injury instead of binding to particular molecular configurations that are typically exposed during cell death or found on the surfaces of pathogens. Interleukin-6 (IL-6), Interleukin-1 β (IL-1 β), and Tumor Necrosis Factor-α (TNF-α) are cytokines that control it. These in turn result in systemic modifications, such as the hepatic release of a variety of plasma proteins, the activation of complement proteins, and different metabolic modifications.(Bansal, Pandey et al. 2014).

2.3-Ferritin

The level of ferritin is a diagnostic indicator for iron-deficiency anemia since it was initially discovered to be an iron-storage protein that buffers iron balance. Serum ferritin has been proposed as a tumor marker in the diagnosis of malignancies since hyperferritinemia has been associated with cancer patients. Recent research has shown that serum ferritin is a multifunctional protein with antioxidant, anti-inflammatory, and anticarcinogenic functions in addition to its function in iron storage.An high serum ferritin level has been linked to pathologic immunosuppression, proliferative disorders, and angiogenesis and may be a sign of cancer. In clinical investigations, the serum ferritin level has been linked to the rate of response to platinum-based chemotherapy in patients with advanced NSCLC, and an elevated serum ferritin level has been independently linked to a worse prognosis for patients with advanced NSCLC. According to a study, high serum ferritin in cancer isn't due to iron overload but rather inflammation and oxidative stress. Patients with NSCLC who had high ferritin and superoxide dismutase levels in their exhaled breath condensate had shorter survival times (Lee, Jeon et al. 2019)

Ferritin Structure A protein that binds to iron, ferritin can be found in both intracellular and extracellular compartments (reviewed in.) As depicted in **Fig.7**, apoferritin creates a roughly spherical structure that stores ferric iron as the mineral ferrihydrite. (The iron-containing version of the protein is known as holoferritin or just ferritin; apoferritin is the iron-free form of the protein.) There are 24 subunits that make up the apoferritin shell. The two subunit types are H and L. The ratio of these subunits varies greatly depending on the kind of tissue and can change under inflammatory and infectious situations. Tissue ferritins range from H-subunit rich to L-subunit rich (found primarily in the heart and kidney) (found predominantly in liver and spleen). Around 450,000 d make up each apo protein molecule. The H monomer weighs 21,000 d and has 182 amino acids, while the L monomer has 174 amino acids and a molecular weight of 18,500 d. (Knovich, Storey et al. 2009)

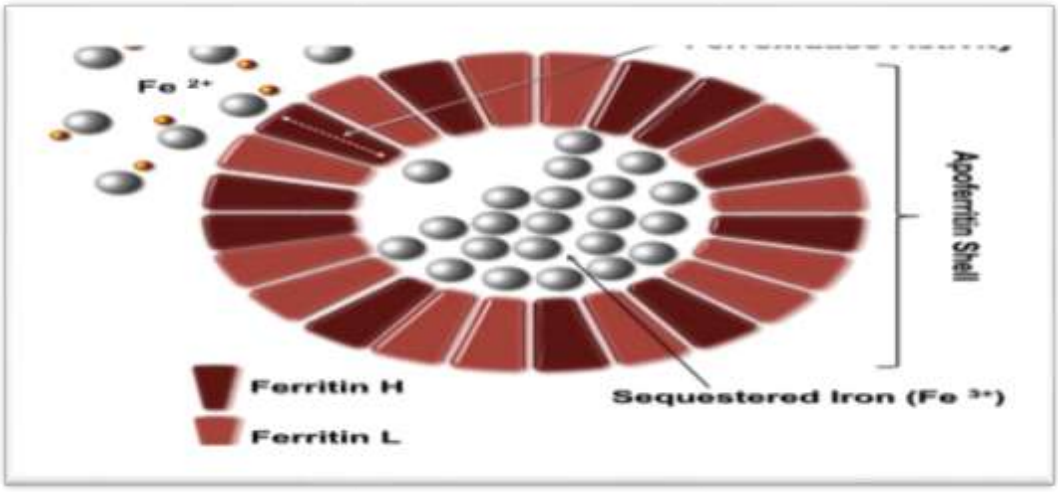


***Fig.7* Structure of ferritin**

Ferritin is a protein that stores ferric iron as the mineral ferrihydrite inside of a roughly spherical structure called apoferritin. The iron-containing form of the protein is known as holoferritin or just ferritin; apoferritin refers to the iron-free version of the protein. The 24 H and L subunits that make up the apoferritin shell have vastly different ratios depending on the kind of tissue and the level of inflammation. Due to its ability to produce reactive species (shown as yellow spheres), which can directly harm DNA and proteins, iron is hazardous in cellular systems. (Knovich, Storey et al. 2009)

3-Relation between covid-19 with parameters

3.1-Relation between vitamin D_3 and Covid-19

Vitamin D promotes vital processes in numerous organs, including the brain, muscle, and immune system, in addition to its well-known function in maintaining calcium and phosphate balance. (Carlberg and Muñoz, 2022). Both innate and adaptive immunity may benefit from vitamin D. Since dendritic cells and macrophages may produce 1,25-dihydroxyvitamin D from 25-hydroxyvitamin D, it has been hypothesized that vitamin D_3 supplementation could enhance dendritic cells and macrophages' abilities, hence enhancing the immune response as a whole. Acute and non-communicable respiratory tract illnesses, particularly viral infections, may be at risk due to vitamin D deficiency. It has been hypothesized that 25-hydroxyvitamin D at optimal serum levels may have immunomodulatory and anti-inflammatory effects and may be helpful for coronavirus illness patients (COVID-19). The advantages of additional vitamin D_3 for COVID-19 patients, however, are still hypothetical and only weakly supported by observational research and short, nonrandomized trials. This randomized clinical trial's goal was to find out how giving vitamin D_3 to hospitalized patients with moderate to severe COVID-19

affected their duration of stay in the facility as well as other important clinical outcomes and side events. The basic assumption was that a single 200 000 IU vitamin D_3 treatment would raise 25-hydroxyvitamin D levels and reduce hospital length of stay. (Murai, Fernandes et al. 2021)

A cheap and secure therapy option that might be added to the current COVID-19 procedures is vitamin D_3 supplementation. Unfortunately, there is yet no conclusive proof that vitamin D_3 supplementation will lessen the severity and/or fatality of COVID-19. In light of this, the primary goal of this study was to assess the safety, tolerability, and efficacy of vitamin D_3 supplementation to shorten the duration and severity of COVID-19 in hospitalized patients who were recruited for a randomized pilot clinical trial to receive either a moderate dose of 2000 International Units (IU)/day of cholecalciferol or a higher dose of 10,000 IU/day for 14 days, in addition to the standard drug therapeutic regimen. (Cervero, López-Wolf et al. 2022)

Such a **Fig.8** Vitamin D is a fat-soluble prohormone that, after being produced in the skin or taken orally, impacts vital bodily processes, such as the control of innate and adaptive immunity. Both canonical and non-canonical pathways can activate vitamin D. It is metabolized by CYP2R1 and CYP27A1 in the liver to 25-hydroxyvitamin D_3 ($25(OH)D_3$), and then by CYP27B1 in the kidney to 1,25-dihydroxyvitamin D_3 ($1,25(OH)_2D_3$), which is physiologically active. This metabolism also takes place in a number of other organs, such as the immune system and the skin. Other systems and organs are harmed in severe COVID-19 instances. (Slominski,Stefan et al 2020)

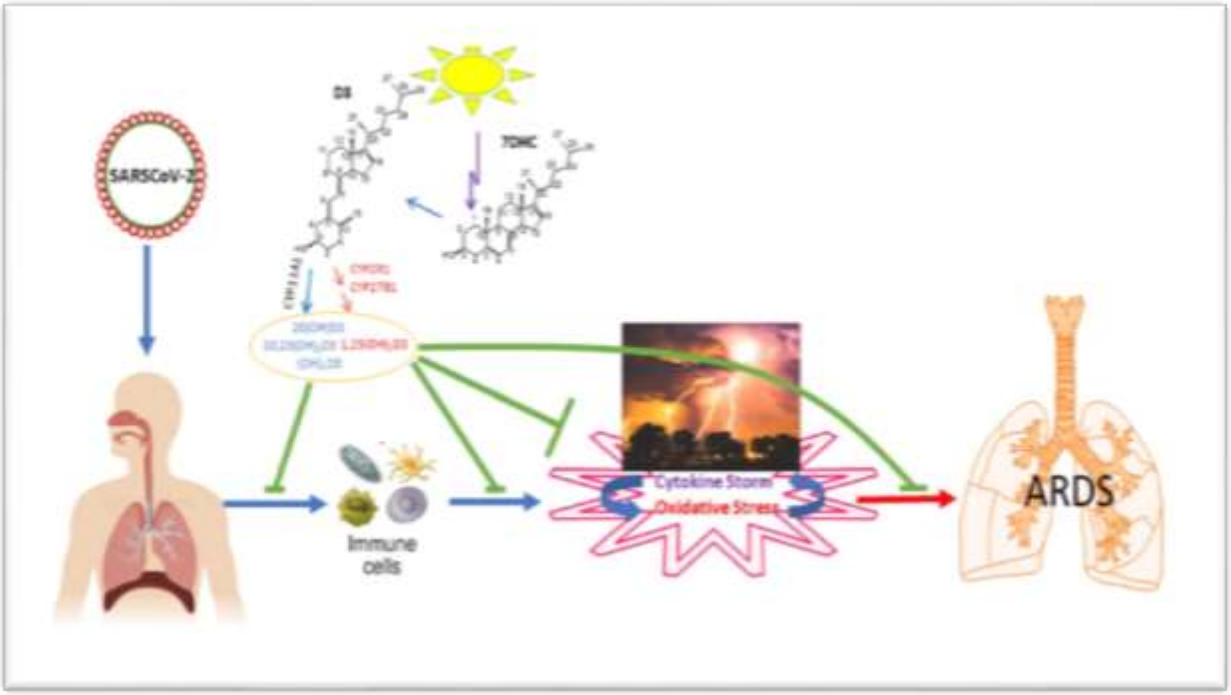


Fig.8 This figure is Hydroxyderivatives of vitamin D_3, by inhibition of cytokine storm and oxidative stress, will attenuate ARDS and multiorgan failure induced by COVID-19.

3.2-Relation between CRP and covid-19

Produced in reaction to the acute inflammatory phase, C-reactive protein is an inflammatory protein of the pentraxin family. In 1930, Tillet and Francis made the initial discovery. And CRP was released between December 2019 and December 2020. Patients with Covid19 that had severely damaged many organ systems and had high levels of CRP were also reported to have perished. (Taha, Shaarawy et al. 2022).

In combination with the inflammatory state present during the disease, CRP activates complement, causes the synthesis of pro-inflammatory cytokines, and causes apoptosis, all of which might have serious consequences. Many medications can lower CRP levels or inhibit its effects, and these may be helpful in the treatment of Covid-19. Elevated CRP levels and Covid19's negative evolution both point to CRP's potential involvement in the cellular damage that causes the infection's failure of several organ systems. Investigation of CRP and other cytokines indicates a relationship between the severity of Covid-19 and these markers. Elevated concentrations of CRP, IL6 (a hepatic CRP inducer), and IL-10 have been utilized as indicators of Covid-19. (Mosquera-Sulbaran, Pedreañez et al. 2021)

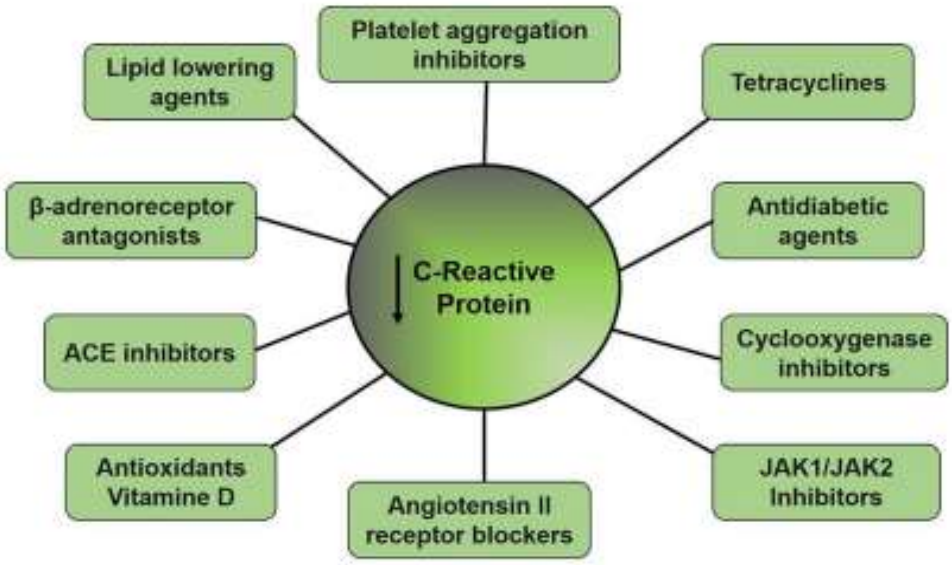


Fig. 9 Pharmaceuticals with the ability to reduce levels of C-reactive protein During Covid-19, SARS-CoV-2 can alter the renin-angiotensin system and induce increased Ang II activity, which induces CRP production with subsequent tissue damage and increased severity of Covid-19. The use of drugs that act by reducing CRP production represents a reasonable therapeutic approach that should be tested in controlled clinical trials.

it is challenging to predict the clinical course and progression of COVID-19 patients' severe condition. Identification of those who may be more susceptible to severe or critical COVID-19, adult acute respiratory distress syndrome (ARDS), young children and adults with Kawasaki-like disease, and even mortality, is becoming more and more important. Together with COVID-19, several laboratory variables have been examined. Particularly elevated levels of C-reactive proteins, erythrocyte sedimentation rate, interleukin-6, and lactate dehydrogenase have been seen. However, in COVID-19 individuals, the overall white blood cell count as well as the eosinophilic and lymphocytic counts have reduced. Increased CRP, lymphopenia, and elevated LDH were recently found to be substantially correlated with the disease's severity. Several laboratory values that were found to be high in cytokine storm (ferritin, procalcitonin, and troponin) may not be available at most hospital labs or are primarily used for research (IL-6). On the other hand, CRP, albumin, and globulin are easily accessible soon after admission and are frequently included in an admission workup in general hospitals, especially in intensive care units (ICU). (Feketea and Vlacha 2020).

COVID-19 is a brand-new viral condition for which there is no known cure, and differences in diameter. The extent of lung lesions and the severity of the disease must therefore be determined by examining biomarkers. In order to determine the value of CRP levels in the early stages of COVID-19 and to associate them with lung lesions and severe presentation, research team evaluated their utility. At the Fever Unit in two areas of Guizhou, China, confirmed cases of COVID-19 were chosen. In addition to measuring the width of the greatest lung lesion in the most severe lung lesion by lung CT scan, CRP levels were taken at the time of admission. Patients were divided into four patient groups: mild, moderate, severe, and critical, and their CRP levels were compared in each group.

A-No. of groups	B- Levels of CRP	C-The diameter of the largest lung lesion
Group one	1-Mild group	(Mann-whitney test = -2.647, -2.171,P < 0.05)
Group two	2-Moderate group	(Mann-whitney test =0.693, -2.177,P < 0.05)
Group three	3-Severe group	(Mann-whitney test = -0.068, -1.549,P < 0.05)
Group four	4-Ceiticl group	(Correlation coefficient =0.873,0.734, P < 0.001)

CRP levels and the diameter of the largest lung lesion in the moderate group were higher than those in the mild group (Mann-Whitney test = −2.647, −2.171, $P < 0.05$), those in the severe group were higher than those in the moderate group (Mann-Whitney test = 0.693, −2.177, $P < 0.05$), and those in the critical group were higher than those in the severe group (Mann-Whitney test = −0.068, −1.549, $P < 0.05$). The difference was statistically significant. CRP levels were positively correlated with the diameter of lung lesion and severe presentation (correlation coefficient = 0.873, 0.734, $P < 0.001$).In the early stage of COVID-19 CRP levels were positively correlated with lung lesions and could reflect disease severity. (Wang, 2020)

3.3-Relation between Ferritin with COVID-19

The goal of this study was to investigate the association between serum ferritin levels at the time of hospitalization and general mortality among COVID-19 patients admitted to a high-complexity university hospital.Also looked into if there is a ferritin cut-off number that could predict death as the ultimate result. This could be very helpful in clinical practice for monitoring mild to severe COVID-19 cases.(Lino, Guimarães et al. 2021)

Although ferritin is frequently used to indicate the whole body iron reserves, its predictive value is associated with COVID-19. The purpose in some study was to evaluate the relationship between ferritin and severity in hospitalized patients with Coronavirus disease 2019 (COVID-19) and to explore the idea that ferritin functions as an independent predictor of mortality.(Ahmed, Ahmed et al. 2021)

The coronavirus disease 2019 (COVID-19) has quickly turned into a pandemic due to ferritin's association with bad prognosis and ability to forecast the progression of COVID-19 patients. Severe COVID-19 individuals had elevated ferritin levels brought on by a cytokine storm and subsequent hemophagocytic lymphohistiocytosis. Consequently, the purpose of this investigation was to ascertain ferritin's function in COVID-19. In order to identify high-risk patients and direct the therapeutic intervention to decrease inflammation, hyperferritinemia, which is produced by excessive inflammation brought on by an infection, is related with intensive care unit admission and high mortality. Serum ferritin levels, a sign of hemophagocytic lymphohistiocytosis and a recognized viral infection consequence, are strongly correlated with poor recovery in COVID-19 patients, and those with worsening lung lesions are more likely to have elevated ferritin levels. The investigations, however, were conducted in a single center or with a tiny sample size. The predictive value of the ferritin level in the chance of a bad outcome in COVID-19 patients thus needs additional confirmation as a pro-inflammatory component in the uncontrolled cytokine storm.In these COVID-19 patients, a quick examination of the patient's state using laboratory testing and clinical evaluation might help clinicians determine the best course of action and order of priority.

Given its possible involvement in diagnosis and prognosis, serum ferritin is particularly intriguing. The current research on COVID-19 was thoroughly examined in this study to ascertain any possible associations between ferritin levels and the severity of the disease, mortality, and other important clinical characteristics of COVID-19 patients. (Cheng, Li et al. 2020)

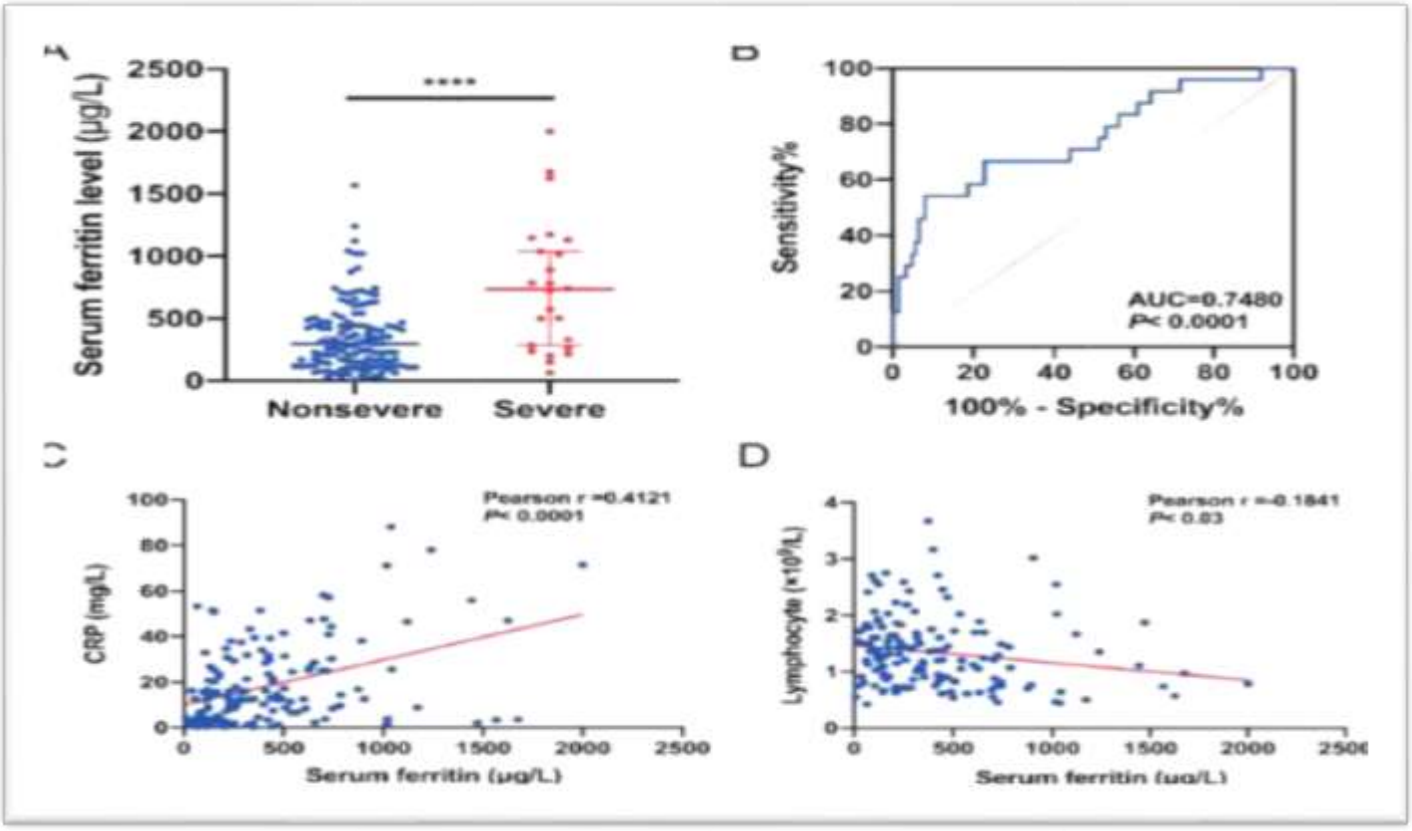


Fig.10 Serum ferritin levels of COVID-19 patients and its correlation with the disease severity. A Serum ferritin levels on admission in severe and nonsevere COVID-19 patients (P< 0.0001). B ROC curve of serum ferritin for the severity of COVID-19. Correlations between serum ferritin and C-reactive protein (**C**), lymphocyte (**D**).

A high serum ferritin level has been shown to be a separate risk factor for the severity of COVID-19 in this retrospective investigation conducted in a Chinese population. To identify COVID-19 patients at high risk, measuring serum ferritin levels during hospitalization may be crucial. (Lin, Long et al. 2020)

It is well recognized that certain COVID-19 patients experience bad outcomes, although the causes of these negative developments are still not entirely understood. However, there is significant doubt over how early clinical or laboratory findings could be related to infectivity and illness severity, aside from how these parameters could help to increase mortality, given that SARS CoV-2 is an unique virus that infects people.

Studies in this regard have demonstrated that the enhanced inflammatory response (cytokine storm) can directly impact organ function in COVID-19 individuals with moderate to severe disease, resulting in decompensation, organ failure, and death. Front Immunol. 2 Garcia LF. Immune response, inflammation, and the clinical spectrum of covid-19 .Towards the end of 2019, the world was quickly hit by the new severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which was first identified in China. Acute respiratory distress syndrome (ARDS), which can be fatal, is one of the worst outcomes of the illness known as COVID-19. By the end of May 2020, COVID-19 had been responsible for about 367,166 deaths since the pandemic's start. The disease's hematological and laboratory manifestations are only partially understood, despite the fact that the number of cases is rising daily. According to the clinical classification from mild pneumonia to severe respiratory failure advised by the World Health Organization and the scientific council in our nation, it is managedPatients with COVID-19 must meet the following criteria: (a) epidemiology history; (b) fever or other respiratory symptoms unrelated to any underlying illness; (c) typical viral pneumonia CT image abnormalities; (d) severe acute respiratory infections; and (e) positive results from an RT-PCR for SARS-CoV-2 RNA.

The condition may be asymptomatic, but it can also manifest as severe ARDS, which is considered to be brought on by an inflammatory cytokine storm. Just before the illness causes pneumonia, the monocyte-macrophage system is already activated. Patients with COVID-19 are shown to have higher ferritin levels throughout this time, along with higher levels of numerous other laboratory indicators such D-dimer and fibrinogen.(Tural Onur, Altın et al. 2021)

4-Conclusion

1- About 100 years have elapsed since the first virus-based pathogens were discovered. As scientists discovered additional diseases brought on by viruses in humans, animals, plants, and microorganisms, there was a general consensus that a virus must be some form of microscopic entity.

2- This virus can spread via droplets in the air. It has not yet been determined where COVID-19's natural reservoir and intermediate host are.

3- Vitamin D_3 controls the parathyroid hormone, adaptive immunity, and cell proliferation processes.

4-dehydrocholestero is exposed to UV radiation. Moreover, plants and fungi generate vitamin D_2, but vertebrates do not. 1, $25(OH)_2D_3$ is mostly produced by photosynthesis, which occurs in the skin.

5-CRP, a pentameric plasma protein, participates in the body's general inflammatory response. It possesses homologs in a wide range of invertebrates as well as vertebrates. It is a molecule that recognizes patterns and is extremely sensitive and non-specific for the acute stage of inflammation.

6- CRP's physiological effects C-reactive protein (CRP) is a factor in the emergence of cardiovascular disease. It is a predictor and marker for cardiovascular disease.

7- A high serum ferritin level has been associated with proliferative problems, angiogenesis, and pathologic immunosuppression and may be an indication of malignancy.

8- It has been proposed that 25-hydroxyvitamin D, at ideal serum levels, may have immunomodulatory and anti-inflammatory effects and be beneficial for those with coronavirus disease (COVID-19).

9- The total white blood cell count as well as the eosinophilic and lymphocytic counts have decreased in COVID-19 patients. Recent research has shown that increased LDH, elevated CRP, and lymphopenia are significantly linked with the severity of the illness.

10- In COVID-19 patients, serum ferritin levels, a marker of hemophagocytic lymphohistiocytosis and a known result of viral infection, are highly associated with poor recovery, and those with increasing lung lesions are more likely to have higher ferritin levels.

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