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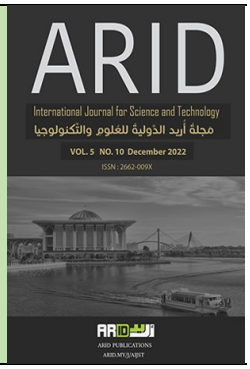

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Some Important Clinical and Biochemical Information about SARS-COVID-2 as a causative agent of Covid-19 disease

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بعض المعلومات المهمة السريرية والمختبرية حول فايروس سارس الثاني المسبب المرضي لمرض كوفيد -19

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ABSTRACT

Severe acute respiratory syndrome coronavirus type 2, SARS-CoV-2 is a disease that causes multi-organ failure in humans and causes physiological changes, which are changes in the components of hematology and biochemical biomarkers that are not specific to Covid-19 disease but considered hallmark into SARS COV-2. Globally, researches indicate that the vast majority of COVID-19 cases fall into the least severe category, i.e., mild to moderate: 81%, severe 14%, and critical 5% of all confirmed cases that infected with SARS COV-2.

الملخص

فيروس كورونا المتلازمة التنفسية الحادة الوخيمة من النوع 2، SARS-CoV-2 هو مرض يسبب فشل أعضاء متعددة لدى البشر ويسبب تغيرات فسيولوجية، وهي تغييرات في مكونات أمراض الدم والعلامات الحيوية البيوكيميائية التي ليست خاصة بمرض Covid-19 ولكن تعتبر السمة المميزة في سارس COV-2. على الصعيد العالمي، تشير الأبحاث إلى أن الغالبية العظمى من حالات COVID-19 تقع ضمن الفئة الأقل خطورة، أي خفيفة إلى معتدلة: 81٪، شديدة 14٪، وحرجة 5٪ من جميع الحالات المؤكدة المصابة بـسارس كوفيد-2..

1.1 Introduction:

In December 31st, 2019, the World Health Organization WHO, China Country Office received notification of instances of pneumonia with an uncertain Etiology (unknown cause) in China [1]. As of 3 January 2020, China's national authorities had reported a total of 44 people with pneumonia of an undetermined cause to WHO; the cause of the outbreak has yet to be determined or confirmed. WHO sought additional information from national authorities in January2020, to assess the risk.[2]

The new SARS 2 virus appeared for the first time in Wuhan, China, in late 2019 in December and spread quickly, which prompted the World Health Organization to declare a state of maximum health emergency in January 2020 and that the disease has become a global pandemic on 11 March 2020 [3]. Before 2019, six types of coronaviruses cause human infection (NL63, OC43, E229, HKU1), in addition to SARS-CoV1 and MERS [4], which infect the upper respiratory tracts as well as the lower respiratory tracts and cause severe symptoms for patients. SARS-CoV-2 is a virus that affects the upper and lower respiratory tracts, resulting in severe acute respiratory syndrome. mainly due to the inflammasome activation and pyroptosis [5].

Literature review 1.2

1.2.1 severe acute respiratory syndrome 2 Coronavirus SARS COV:

Severe acute respiratory syndrome 2 Coronavirus (SARS COV-2) is considered the virus that causes COVID-19 disease [6]. From time-to-time COVID-19 launch in Wuhan, Hubei Province, China, from time to time, members of the Coronavirus family appear to cause infections in humans, but not of the same importance as Covid 19, such as HCoVs, SARS –CoV, MERS-CoV. Reported symptoms include fever, cough, fatigue, pneumonia, headache, diarrhea, hemoptysis, and dyspnea [3].

1.2.2 Classification:

The virus is a Zoonotic source, as is for the infection to occur, it must be passed from animal to human [7]. Until this moment, all research and studies indicate that the SARS CoV-2 is of animal origin (Zoonotic disease).

SARS COV-2 has the same clinical features and genetic information as SARS and MERS, as they both belong to the same family of beta-coronavirus [3]. And there is congruence in terms of the sequence of nucleotides. There is also a great similarity of 79.5% between SARS COV-2 and the SARS COV-1 virus [8]. All seven HCOV (OC43-NL63, E229, HKU1, MERS, SARS COV, and SARS-COV2) have a Zoonotic origin such as mice, pangolin, bats, and other pets. They have been classified into four different genera according to their genomic and protein sequences Alpha, Beta, Gamma, and Delta. The two genera (E229-NL63) are alpha, while the other five are beta [9]. The family Coronaviridae is organized into 2 subfamilies, 5 genera, 26 subgenera, and 46 species [6].

Category: Coronaviruses

Realm: Riboviria

Order: Nidovirales

Suborder: Cornidovirineae

Family: Coronaviridae

Subfamily: Orthocoronavirinae

Genus: Betacoronavirus

Subgenus: Sarbecovirus

Species: *Severe acute respiratory syndrome-related coronavirus*

Individuum: SARS-CoV-2

1.2.3 SARS COV-2 Structure:

SARS COV-2 is similar to other genera of the Coronavirus family in that it consists of a single strand, unsegmented, sense positive RNA genome. There exist as well as similarities in the localized coding regions and non-coding regions [19,20]. SARS COV-2 has a diameter of about 50-200 nanometers [10]. And like any family coronavirus, it consists of a genome and covers that surround it.

Kim D *et al* [22] found that up to 29 proteins are encoded by the SARS-CoV-2 genome, given that some segments are not expressed [11].

Where the genome is surrounded by a structure called the nucleocapsid (N). The membrane (M), the envelope (E), and the spikes (S) are the basic structure of the virus [12].

Both SARS -1 and SARS-2, which are the new addition to the human coronavirus family, include (OC43, NL63, HKU1, and MERS) which belong to the genus β-Coronavirus, and (229E and NL63) that belong to the genus of α-Coronavirus which contains a polycistronic genome. It encodes for the structural proteins that are included in the phenotype of the virus, along with the accessory proteins in the last third of the RNA strand. It also interferes with the manufacture of proteins that are not related to the formation of the structure of the non-structural proteins (nsp) virus near the N-end of the genome [13]. Thus, the SARS COV-2 genome consists of 29,903 nucleotides containing 16 open reading frames [14].

Thus, [26] analyzed the SARS 2 genome which consists of 29,903 nucleotides containing 16 open reading frames (ORFs). The role of (ORF1a) (ORF1b) is to encode multiple proteins (pp1a) and (pp1b), both of which work through the mechanism of changing the ribosomal frameshift on the cleavage of the virus protease into 16 regions named non-structural protein (nsp). (ORF1a) encoded from 1 to 11(nsp) and (ORF1b) encoded from 12 to 16 nsp. In the last third, near the carboxyl end, it encodes the basic components of the virus, which are the spike, envelope, membrane, and nucleocapsid protein. Among the main combinations, there are a series of accessory genes (ORFs 3a, 3b, 6, 7a, 7b, 8b, 9b, and 16) which encode the accessory proteins that regulate infection and evade immunity but which do not incorporate with SARS COV-2 genome [2].

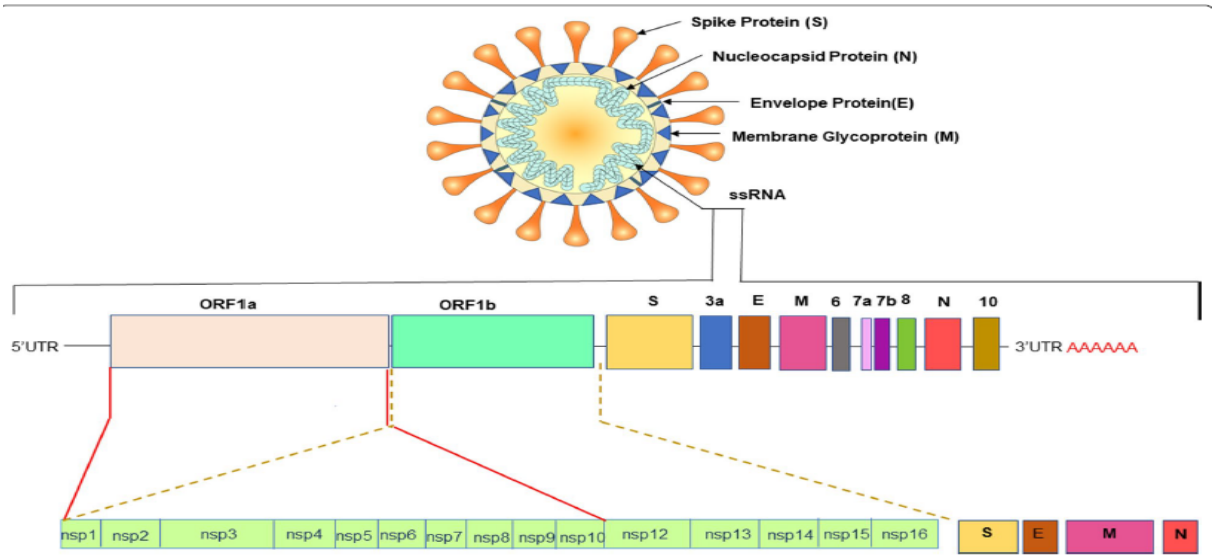


Fig.1.2 The SARS-CoV-2 genomic structure is depicted schematically. The structure of SARS-CoV-2 is spherical. A lipid envelope surrounds the virus, which is covered in spike glycoprotein. The genomic arrangement of SARS-CoV-2 is typical of Betacoronavirus. The full-length RNA genome is roughly 29,903 nucleotides long, and the 5′UTR contains open reading frame (ORF1a and ORF1b). Thensp1–nsp10 is encoded by ORF1a, while nsp1–nsp16 is encoded by ORF1b. The structural proteins are encoded by four genes: the spike gene, the envelope gene, the membrane gene, the nucleocapsid gene, and a poly (A) tail at the 3′UTR. The auxiliary genes are strewn among the structural genes [9].

1.2.4 Pathogenicity:

In general, viruses depend on the cell to produce many new virus copies of the same type, since the virus is obligated to parasitize. Once infecting a sensitive cell. Cell resources are harnessed for virus reproduction. A cell is considered infected if the virus attaches itself to the special receptor on the cell membrane and enters the cell. And this process is carried out by proteins specific to the virus [15].

For SARS COV-2, its life cycle begins when (S) protein is activated by two proteins, by the cellular serine protease (TMPRSS2) and trypsin-like protease from airways (TMPRSS11D). Protein S binds itself to the angiotensin-converting enzyme 2 (ACE2) receptor [12], [16]. The ACE2 enzyme that is targeted by SARS CoV-2 is a homeostatic enzyme, which is responsible and controlling for the isometric pressure balance of extracellular fluids as well as arterial

pressure in humans. It is found mainly on the ciliated cells of the upper airway epithelium, tubular cells near the kidneys, the duodenum, small intestine, liver, Sertoli cells, Leydig cells of the testis, and glandular cells of the gallbladder. It is also present in the epididymis and cardiomyocytes, in the tissues of the heart, pancreas, seminal vesicles, and placenta [17].

The fusion between a host cell and SARS COV-2 occurs in an endosome fashion when a conformational change occurs between the virus's S protein and angiotensin-converting enzyme 2 (ACE2). Then SARS COV-2 RNA is injected into the cytoplasm of the host cell to be translated by the ribosomes into multiple viral repeat proteins pp1a-pp1b, which are then processed by 3CLpro and PLpro proteases is an essential coronavirus enzyme that is required for processing viral polyproteins. This enzyme generates a functional replicase complex and enables viral spread, from this fission, 16 NSPs are produced, which are accused of producing the transcription and replication genes of the virus [18].

Whereas, structural proteins and accessory proteins are synthesized by translating the positive RNA template into the negative RNA strand to produce the mRNA. Finally, the RNA genomic and viral proteins are surrounded by the structural proteins of SARS-CoV-2, this role is played by the Golgi apparatus and the rough endoplasmic reticulum [18], [19].

1.2.5 Immune response of Covid-19:

Unlike most other respiratory infections SARS-CoV2 is unique in its incidence curve. The severity of SARS-CoV-2 infection increases with age. It is also different from most other respiratory diseases that have a curve similar to the (U) shape. That is, it threatens the edges of the curve, which represent young and old ages. While the youth group is less vulnerable to infection and more protected from it [20]. Utilizing convalescent plasma may help patients recover more quickly or decrease / prevent disease-related SARS-COV2 [21].

In addition to knowing the body's immune response against SARS-CoV2 and its role in the severity of infection, it is important for us in designing an appropriate and effective vaccine, as well as finding the appropriate treatment for the virus. Two types of immune response occur inside the body: a weak primary response to Interferons, which allows the virus to multiply, and a severe secondary or late immune response characterized by a massive of pro-inflammatory cytokines, including interleukins IL6, IL1, TNF, MCP-1, and IP-10 proteins [22]. Further,

neutrophils and macrophages, that generate an immune response and a strong reaction in some Cases are destructive and harmful to the patient's body [11].

1.2.5.1 Innate immune response:

SARS-CoV2 infection begins when the virus binds itself by a spike protein S1 to its receptor on the cell surface called the ACE2receptor [23].

[53] focus that the virus injects its genome into the cell then the ribosomes make new copies of the virus, and then the Golgi apparatus and the rough endoplasmic reticulum manufacture the envelopes of the virus in the order it to exist outside the cell and infect other cells [24].

When the virus genome enters the cell, the pattern-recognition receptors PRRs on the surface of the infected cell (such as TLR 4), endosomal Toll-like receptors TLR3 and TLR7, and cytosolic receptors (MDA5and RIG I) recognize the SARS-CoV2 RNA. Thus, they activate a series of reactions downstream signaling cascade including NF-kB, IRF3, and IRF7 and their nuclear translation. These transcription factors lead to an activity-inducing gene transcription for (α) and (β) IFN and pro-inflammatory cytokines [25].

1.2.5.2 Toll-like receptors:

TLRs are a type of pattern recognition receptor (PRR) that triggers the innate immune response by detecting conserved molecular patterns that allow early pathogen detection [26]. TLRs are type I transmembrane proteins with three structural domains: a leucine-rich repeats (LRRs) motif, a transmembrane domain, and a Toll/IL-1 receptor (TIR) domain in the cytoplasm. The TIR domain interacts with signal transduction adaptors and initiates signaling, whereas the LRRs motif is important for pathogen recognition [27].

[57] explained thatinvasion of a virus triggers the host's innate immune response, which produces a variety of cytokines and Interferons to help eradicate infections. Viral proteins, in addition to viral DNA/RNA, are targets of pattern recognition receptors. Toll-like receptors TLR1, TLR2, TLR4, TLR6, and TLR10 are membrane-bound receptors that recognize viral proteins [28].

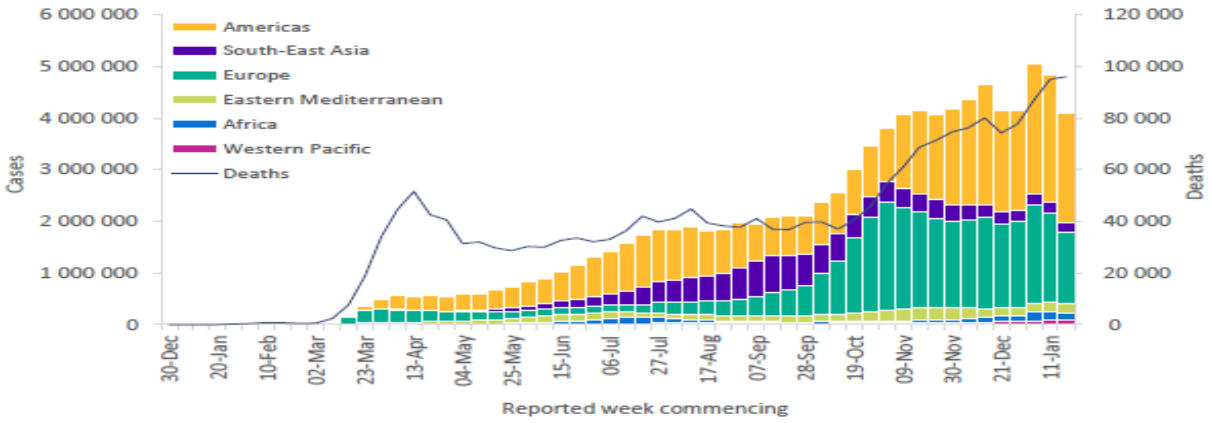
1.2.5.3 Adaptive immune response:

The second aspect of immunity is T cell and B cell that plays a major role in adaptive immunity. CD4 cells guide and develop the immune response to antibodies while the role of CD8 cells is to kill the virus directly. Immunogenic CD4 and CD8 T cell epitopes in SARS and MERS patients were found to localize mainly to structural proteins, particularly the S protein [29], [30].

Virus particles and/or cell debris affected by virus infection are recognized by dendritic cells in the lung. From there they go to the lymph nodes and present these antigens to CD4 and CD8 cells, which have an important role in activating innate and adaptive immunity. When antigen reaches the lymph nodes, the macrophages in the lymph nodes produce cytokines, including Interferons and interleukins such as interleukin-12. Dendritic cells DCs activate CD4 T lymphocytes in the presence of IL-12, causing them to develop into Th1 effector cells. This produce IL-2 and IFN gamma, which aid in the differentiation of CD8 T lymphocytes and B lymphocytes into cytotoxic cells and immunoglobulin M-producing plasmocytes [31], [32].

1.2.6 Epidemiology:

The new SARS 2 virus appeared for the first time in Wuhan, China, in late 2019 in December and spread quickly, which prompted the World Health Organization to declare a state of maximum health emergency in March 2020 and that the disease has become a global



pandemic [3] Fig:(1.2.1)

Figure 1.2.1: COVID-19 cases mentioned weekly by WHO area, and global deaths, as of 24 January 2021 (WHO, 2021).

Patients have reported a high fever (above 38°C), a dry cough, lethargy, and breathing problems. The disease has been termed COVID-19 and has been connected to a seafood market in Wuhan, China [34], [35]. It rapidly spread to neighboring Far Eastern countries, followed by the Middle East and Europe. Pneumonia, septic shock, metabolic acidosis, and bleeding are all symptoms of the condition in severe situations [36]. The incubation time is anticipated to be between 5 to 14 days and varies from one patient to another depending on age and infected date [37]. The virus has infected more than 150 countries and areas around the world as of March 16, 2020.

Abbreviations:

ACE2: Angiotensin-converting enzyme 2.
COVID19: Coronavirus disease 2019.
ORF: Open reading frame.
SARS2: Severe acute respiratory syndrome coronavirus 2.

Conclusions:

- So far, SARS-CoV is considered an animal source virus.
- There is a great similarity between SARS-CoV-A and the viruses that preceded it from the same strain, in varying proportions.
- Innate immunity plays an important role in determining the patient's condition through the release of cytokines and the rise of neutrophil cells. Adaptive immunity also plays an important role.

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