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Review

Historical Perspectives of SARS-CoV-2 Viral Subversion of Host Cell: Biochemical and Pathological Aspects

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Abstract: The pandemic of coronavirus disease-19 (COVID-19) was a worldwide health crisis affecting many more people than 221 countries causing life-threatening complications and indirectly affecting even more individuals through disruption of daily living. COVID-19 is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which is a member of beta-coronavirus having RNA as a genetic material sharing 79% similarity with the bat SARS-CoV genome. The SARS-CoV-2 enters the host cells by binding specifically to the angiotensin-converting enzyme-2 (ACE-2) which is expressed on the surface of epithelial cells in the respiratory tract, intestine, kidneys, and others causing severe acute respiratory failure and other complications. In addition to respiratory symptoms, uncontrolled SARS-CoV-2 infection can induce a cytokine storm, whereby pro-inflammatory cytokines and chemokines such as IL-6, TNF-α, and IL-1β are increased, which in turn leads to multiorgan damage. Herein, we described the history and classification of coronaviruses, geographical distribution of COVID-19, SARS-CoV-2 structure and genomic organization, life cycle, immunopathological responses, symptoms, and finally pulmonary and extra-pulmonary complications of SARS-CoV-2 infection.

***Keywords*:** SARS-CoV2 infection, COVID-19, life cycle, immunological responses, COVID-19 complications

1. Introduction

Human beings are under constant attack from invading microbes including viruses which are submicroscopic contagious agents that replicates only within the cells of living organisms and are fully dependent on the host cells' translational machinery to synthesize their polypeptides that are substantial for the replication of virus; therefore the host responses to invading viruses determine the outcome of these infections [1].

World Health Organization (WHO) China Country Office was informed on December 31, 2019, that there are several cases of pneumonia of obscure causes appeared in Wuhan, Hubei Province, China, and then, on January 9, 2020, China Center for Disease Control and Prevention declared that the reasonable factor was a new coronavirus identified as 2019-nCoV (i.e., 2019 Novel Coronavirus), which is phylogenetically similar to SARS-CoV and within few months the virus spread rapidly around the world [2]. Therefore, WHO reported on March 11th, 2020, that the new official name for the epidemic disease caused by 2019-nCoV was coronavirus disease or COVID-19 and the International Committee on Taxonomy of Viruses renamed 2019-nCoV as severe acute respiratory syndrome coronavirus-2 (SARS-

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CoV-2) [3-4]. On July 01, 2023, there were 690,956,914 cases and about 6,895,913 deaths were reported in about 222 countries [5]. The SARS-CoV-2 outbreak is a major global challenge, causing a serious healthcare crisis even in regions with developed healthcare systems therefore scientists from different disciplines are working hard to assess the situation and control this crisis [6]. The clinical manifestations of severe COVID-19 patients are hypoxia and dyspnea with fast deterioration to acute respiratory distress syndrome (ARDS) [7], acute renal failure [8], hypercoagulability and coagulopathy [9], cardiovascular complications [10], and others. Therefore; this narrative review will focus on the history and classification of coronaviruses, COVID-19 geographical distribution, SARS-CoV-2 structure and genomic organization, life cycle, immunopathological responses, symptoms, and finally pulmonary and extra-pulmonary complications of SARS-CoV-2 infection.

1.1 *History and classification*

Coronaviruses are a large family of viruses which can infect avian and mammalian species, including humans. The first coronavirus to be discovered was the avian infectious bronchitis virus (IBV) identified by Schalk and Hawn [11] in 1931. The first human coronaviruses were identified in 1966 by Tyrell and Bynoe as positive single-stranded, enveloped RNA (+ve ssRNA) viruses with a genomic size of 26-32 kb, which can infect both humans and mammals [12]; then Tyrell et al. in 1968 coined the name "coronavirus" which is derived from the "corona"-like (crown-like) morphology characterized for these viruses under the electron microscope [13].

Coronaviruses belong to *Nidovirales* order and *Coronaviridae* family. In June 2005, the Coronaviridae family was divided into two subfamilies, *Coronavirinaea* and *Torovirinae* [14]. Then; *Coronavirinaea* was further subdivided based on serology and phylogenetic clustering into different four genera, Alpha (α)-coronavirus, Beta (β)-coronavirus, Gamma (γ)-coronavirus and, Delta(δ)-coronavirus [15]; as depicted in Figure 1.

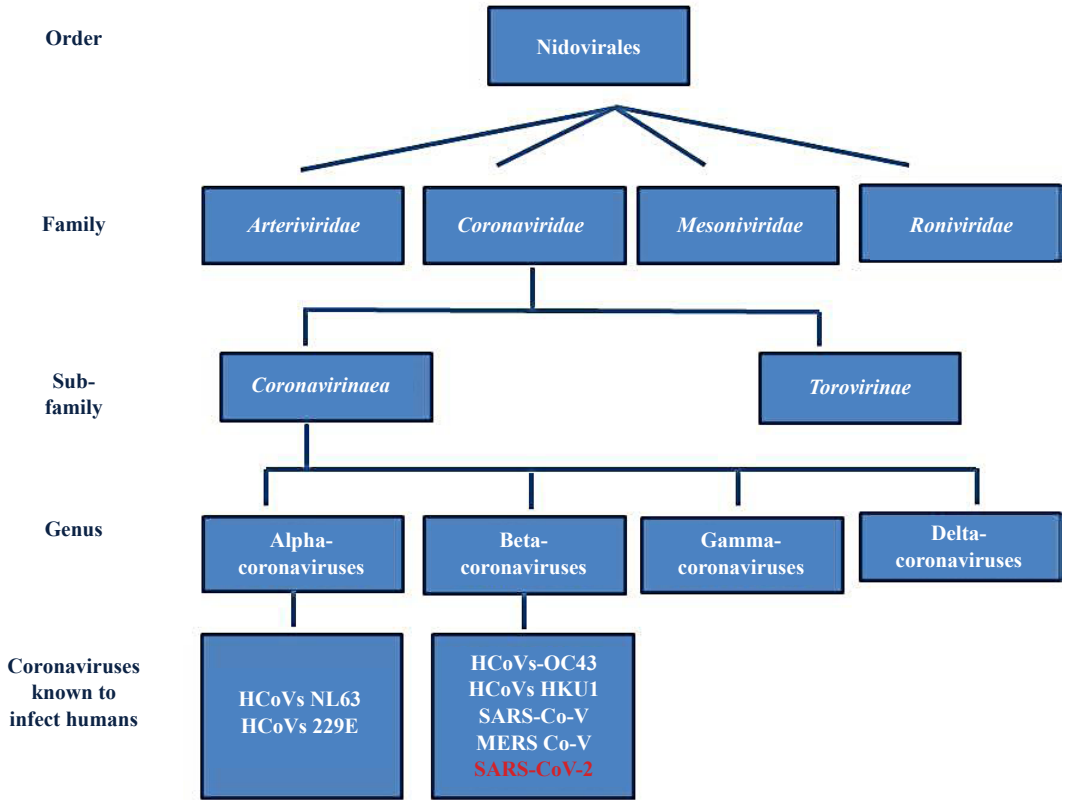


Figure 1. Taxonomy of Coronaviruses

Alpha- and Beta-coronaviruses mostly infect humans and mammal [16] and Beta-coronaviruses are the most fatal one, in particular, including till now three pandemic viruses which are SARS-CoV, MERS-CoV [17-18], and finally SARS-CoV-2. While Gamma-coronavirus, and Delta-coronavirus mostly infect birds and fish [19].To date, only seven human coronaviruses were identified; two alpha-coronaviruses **HCoVs-NL63** and **HCoVs-229E** and five beta-coronaviruses **HCoVs-OC43**, **HCoVs-HKU1**, **SARS-CoV**, **MERS-CoV** and finally **SARS-CoV-2** [20].

Till now; there are three human coronaviruses are reported in the WHO Blueprint list due to their potential to cause epidemic diseases and the absence of effective therapies:

(1) In November 2002, in Guangdong, China; Severe Acute respiratory syndrome coronavirus (**SARS-CoV)** was first recognized in humans and then worldwide spread to 29 countries, resulting in 8098 confirmed cases and 774 deaths with a mortality rate of 9.6%. In July 2003, the SARS epidemic ended and there is no new cases of SARS have been identified since 2004 [21].

(2) In 2012, in Saudi Arabia; the Middle East respiratory syndrome coronavirus (**MERS-CoV**) was first identified and continues to cause human disease with sporadic community cluster outbreaks in the Middle East. On Feb 29, 2020, there were 2,494 confirmed cases and 858 deaths with a mortality rate of 34.4% identified in 27 countries, the majority of which were reported by Saudi Arabia (2,106 cases, 780 deaths) [22].

(3) In December 2019, SARS-CoV-2 which was first discovered in China and then spread rapidly worldwide, causing till April 2021, more than 138,519,964 cases and about 2,477,373 deaths were reported in about 222 countries, with a mortality rate of 2-5%. The transmission and spread of SARS-CoV-2 did not follow the pattern of other respiratory viruses and in spite of its lower mortality rate that has been estimated until now, the higher ability of transmission of SARS-CoV-2 over **SARS-CoV** and **MERS-CoV** is a determinant factor of its pathogenic danger.

1.2 *Geographical distribution of COVID-19*

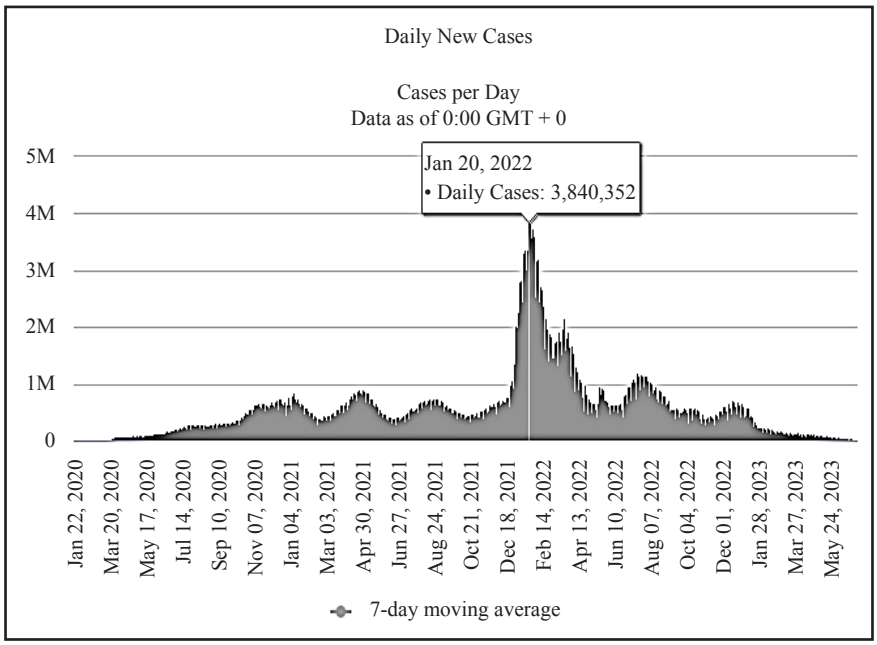


Figure 2. Daily new cases of SARS-CoV-2 infection from the beginning till June 2023, the highest number was 3,840,352 on Jan. 20, 2022

As mentioned before and according to worldomerter's reports [5], till July 01, 2023, a total number of 690,956,914 cases of SARS-CoV-2 infection have been confirmed worldwide, with a total of 6,895,913 deaths. As shown in Figure 2, the highest number of SARS-CoV-2 infection cases was 3,840,352 on Jan. 20, 2022. The top 10 countries in worldwide with the highest burden of SARS-CoV-2 infection were the United States of America (USA), India, France, Germany,

Brazil, Japan, S. Korea, Italy, United Kingdom (UK) and Russia; while for Africa, South Africa was ranked as the first country then, Morocco, Tunisia, Egypt, Libya, Ethiopia, Réunion, Zambia, Kenya, and Botswana; as depicted in Table (1A).

Table 1. The top 10 countries worldwide and Africa affected by SARS-CoV-2 infection till January 01, 2022

Worldwide		Africa	
Country	No. of cases	Country	No. of cases
A. According to the total number of confirmed cases of SARS-CoV-2 infection			
USA	107,312,026	South Africa	4,076,463
India	44,994,228	Morocco	1,275,136
France	40,138,560	Tunisia	1,153,361
Germany	38,428,685	Egypt	516,023
Brazil	37,671,420	Libya	507,266
Japan	33,803,572	Ethiopia	500,920
S. Korea	32,131,606	Réunion	486,588
Italy	25,897,801	Zambia	347,022
UK	24,618,436	Kenya	343,537
Russia	22,959,198	Botswana	330,008
B. According to the total number of deaths of SARS-CoV-2 infection			
USA	1,168,149	South Africa	102,595
Brazil	703,964	Tunisia	29,423
India	531,906	Egypt	24,613
Russia	399,563	Morocco	16,297
Mexico	334,336	Ethiopia	7,574
UK	226,278	Algeria	6,881
Peru	220,695	Libya	6,437
Italy	190,868	Zimbabwe	5,707
Germany	174,352	Kenya	5,689
France	167,642	Sudan	5,046

The top 10 countries in worldwide with the highest fatality of SARS-CoV-2 infection were the USA, Brazil, India, Russia, Mexico, UK, Peru, Italy, Germany, and France; while in Africa, South Africa then Tunisia, Egypt, Morocco, Ethiopia, Algeria, Libya, Zimbabwe, Kenya and Sudan; as depicted in Table (1B).

1.3 *SARS-CoV-2 structure and genomic organization*

By using the electron microscope; it was found that SARS-CoV-2 is an enveloped virus of particle size 70-140 nm and its long RNA genome is tightly packed into the center of the particle, and surrounded by a protective nucleocapsid (N). SARS-CoV-2 core particle is further surrounded by an outer membrane envelope derived from the cells in which the virus is last assembled but is modified to contain specific viral proteins, including the spike (S), membrane (M), and envelope (E) proteins [23]; as shown in Figure 3(a).

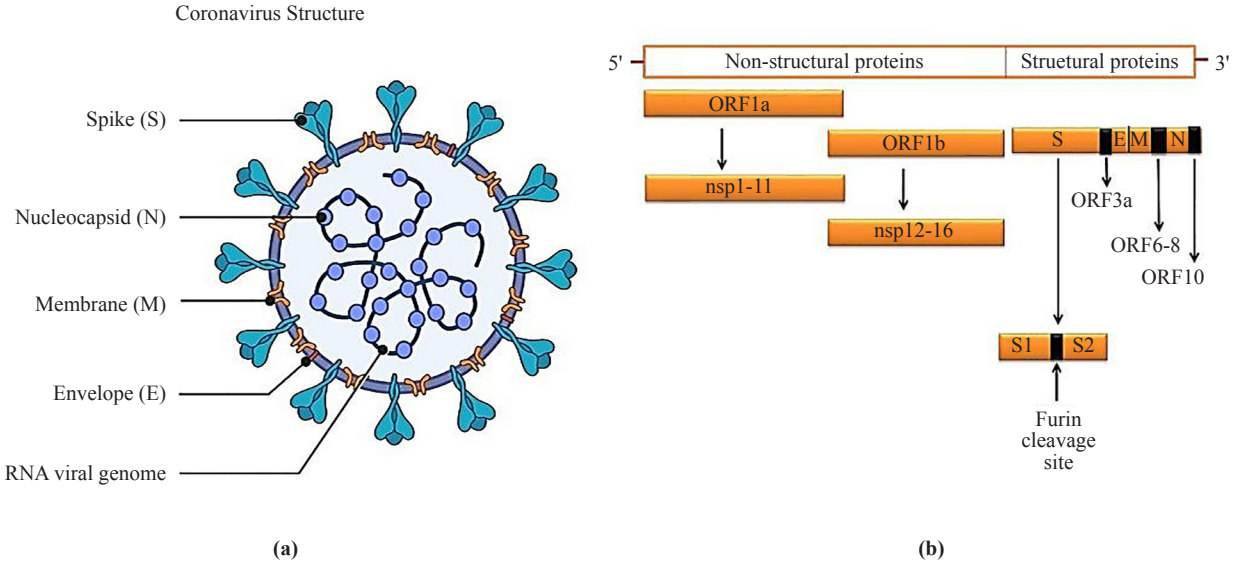


Figure 3. SARS-CoV-2 structure and genomic organization. (a): Structure of SARS-CoV-2, (b): SARS-CoV-2 genomic organization

Coronaviruses are enveloped and non-segmented positive single strand (+ss) RNA viruses of 50-200 nm diameter and ~ 30 kb genome, which is the biggest reported viral RNA genome till now. SARS-CoV-2 is tightly rooted from the β-lineage of bat coronaviruses, as revealed by the phylogenetic analysis which found that SARS-CoV-2 whole genome shares 79% genetic similarity with that of SARS-CoV and is 98% identical to the bat coronavirus BatCoV-RaTG13 [24].

The characterization of the SARS-CoV-2 entire genome has been achieved by using an RNA-based low-input metagenomic next-generation sequencing (mNGS) approach and the results revealed that 29,903 nucleotides positive-strand RNA genome of the SARS-CoV-2 encodes ~30 known and candidate mature proteins [25]. Like other coronaviruses, the SARS-CoV-2 genome is a positive single-strand (+ss) RNA of a 5'-cap and a 3'-poly-A tail and therefore can act as a mature mRNA, permitting its translation directly from the host translation machinery [26].

As shown in Figure 3b; the genetic material of SARS-CoV-2 is a polycistronic mRNA with 5'-cap and 3'-poly-A tail, 5'-end of SARS-CoV-2 presents a frameshift between two open reading frames (Orfs), Orf1a and Orf1b, allowing the synthesis of two different polypeptides (pp1a and pp1ab) which are further proteolytically break down into 16 non-structural proteins (nsp1-11 and nsp12-nsp16). Non-structural proteins are supposed to be involved in the virus infection cycle [27]. The 3'-end contains the sequence necessary for the production of the structural proteins, which are spike glycoprotein (S), envelope protein (E), membrane protein (M) and nucleocapsid protein (N) [28]. The 3'-end also encodes nine accessory proteins; which are Orf3a, Orf3b, Orf6, Orf7a, Orf7b, Orf8, Orf9b, Orf9c and Orf10; which are believed to play important roles in host interaction and virulence [29]. It was noted that the SARS-CoV-2 genome lacks

the hemagglutinin-esterase (HE) gene, which is characteristic of Betacoronaviruses lineage A [30]. Functions of the non-structural proteins and accessory proteins in the pathogenesis were summarized in Table (2).

Table 2. Functions of SARS-CoV-2 non-structural proteins and accessory proteins in the pathogenesis

Protein	Functions	Reference
	A. Non-structural proteins (nsps)	
nsp1	• Small protein (179 amino acids), is the first to be produced by the virus and plays an important role in suppressing the host cell immune response, thereby allowing the SARS coronavirus to infect and replicate freely. • Also, it blocks host cell translation by binding to the ribosome's 40S subunit, thereby inactivating their translation functions and promoting cellular mRNA degradation.	[31-32]
nsp2	• Binds with two host proteins, prohibitin1 and 2 (PHB1 & PHB2), which interact with various transcription factors modulating transcriptional activity.	[33]
nsp3	• The biggest encoded viral protein (1,945 amino acids). • Contains two transmembrane regions, TM1 and TM2, along with eight domains: Ubl1 and Ubl2, Glu-rich, PL2pro, nsp3 ectodomain (3Ecto), macrodomain (X), CoV-Y and Y1 domains. • Responsible for cleaving nsp1, nsp2 and itself from polyproteins. • Interacts with other nsps and the RNA, modifies the host proteins such as RCHY1, and therefore supports viral survival. • Blocks the host's innate immune response by de-ubiquitination.	[34-35]
nsp4	• It is a transmembrane scaffold protein, important for the proper structure of double-membrane vesicles (DMVs).	[36]
nsp5	• The main viral protease, also known as 3CLpro or Mpro, cleaves viral polyproteins pp1a and pp1b at 11 sites. • Inhibits IFN induction.	[37]
nsp6	• Induces the formation of endoplasmic reticulum (ER)-derived autophagosomes and therefore removes the host proteins involved in viral replication inhibition. • Induces double-membrane vesicles	[38-39]
nsp7	• Forms complex with nsp8 and nsp12 to produce the RNA polymerase activity.	[40]
nsp8	• Makes heterodimer with nsp7 and 12 to produce the RNA polymerase activity.	[40]
nsp9	• It is a ssDNA/RNA-binding protein. • May bind to helicase and therefore, favors efficient viral growth and replication.	[41]
nsp10	• Interacts with nsp14 and nsp16 and forms nsp10-nsp14 and nsp10-nsp16 complexes, thereby stimulates their ExoN and RNA Cap 2-O-methyltransferase activities; • Contributes to viral replication fidelity	[42]
nsp11	• Consists of 13 amino acids identical to the first segment of nsp12. • Its function is still unknown.	-
nsp12	• RNA-dependent RNA polymerase (RdRp) binds to its essential cofactors, nsp7 and nsp8 to assemble the RNA-synthesis complex	[43]
nsp13	• RNA helicase. • Also involved in the mediation of RNA 5'-triphosphatase activity, thereby suggesting its involvement in capping viral RNAs.	[44]
nsp14	• Bifunctional protein having exoribonuclease activity in the N-terminal domain, and N7 methyltransferase activity in the C-terminal domain. • It is proposed to be involved in proofreading, repair and recombination of the coronavirus genome. • Interferes with IFN-induced antiviral activity.	[45-46]
nsp15	• It is a $Mn2^{+}$-dependent viral endoribonuclease. • Evades RNA sensing.	[47]
nsp16	• Forms nsp10/nsp16 complex and is responsible for executing 2'-O-methyltransferase activity. • Shields viral RNA by forming a protective cap that prevents recognition by either MDA5 or IFIT proteins. This capping process permits viral infection with reduced host recognition and, consequently, robust viral replication in the absence of the host cell's innate immune response.	[48-49]

Table 2. (cont.)

Protein	Functions	Reference
	B. Accessory proteins	
ORF3a	• Located in between the S and E genes, and is the largest accessory protein of SARS-CoV-2, consisting of 274 amino acids. • Possessing three transmembrane domains, forms dimer and its six transmembrane helices together create ion channels on the host cell membrane, which is highly conducive for Ca^{2+}/K^{+} cations compared to Na^{+} ion. • Involved in virus release, apoptosis and pathogenesis.	[50]
ORF3b	• Inhibits the synthesis of type 1 IFNs (IFN-alpha/beta), which are the major components of the innate immune response.	[51-52]
ORF6	• Is a 61-amino acids long membrane-associated protein. • Is present in the ER and Golgi compartments in virus-infected cells. • Suppresses the induction of type 1 IFN and IFN signaling pathways	[53]
ORF7a	• Is a 122-amino acids type-I transmembrane protein. • It contains a 15 amino acids signal peptide sequence, an 81 amino acids luminal domain, 21 amino acids transmembrane domain and a short C-terminal tail. • Induces apoptosis and immune response by activating NF-κB and the IL-8 promoter.	[54]
ORF7b	• Is a 44-amino acids integral membrane protein expressed in SARS-CoV-infected cells wherein it remains localized in the Golgi compartment.	[55]
ORF8	• Consists of 121 amino acids, the 1-17 residues comprise the N-terminal signal sequence, which is essential for transport to ER. • Interacts with major histocompatibility complex-I (MHC-I), thereby mediating their degradation in cell culture, and therefore may help in immune evasion.	[56]
ORF9a	• Consists of 97 amino acids. • Tends to associate with the adaptor protein, TOM70, and thereby suppresses IFN-I to mediate antiviral response.	[57]
ORF10	• Located downstream of the N gene and has been detected in infected cells.	[58]
ORF14	• It is made up of 73 amino acids and is synthesized by leaky scanning of the N gene. • Its function is not clearly understood.	[59]

1.4 *Life cycle of SARS-CoV-2*

The life cycle of SARS-CoV-2 inside the host cell comprises six stages, as represented in Figure 4.

1.4.1 *Virus entry*

Among SARS-CoV-2 structural proteins, the spike (S) protein-glycoprotein and spike-like protrusions present on the coronavirus's transmembrane-has necessary roles in the attachment and entry of the virus and subsequently COVID-19 pathogenesis [60-61]. The viral life cycle initiates when the receptor-binding domain (RBD) at the N terminus of the S1 subunit of S protein binds to angiotensin-converting enzyme 2 (ACE2) which is expressed on the surface of epithelial cells in the respiratory tract, intestine, kidneys and others [62]. The RBD in S1 is the most variable part of the coronavirus genome; in SARSCoV-2, there are five crucial amino acids-L455, F486, Q493, S494, N501, and Y505- which give high affinity to the RBD towards the extracellular domain of human ACE2, causing the natural selection to human host or other mammals having human-like ACE2 [24].

The S protein of SARS-CoV-2 has two characteristic features that are absent in SARS-CoV: Firstly it has a high affinity to bind human ACE2 receptor, which seems to be linked to the increased transmissibility of SARS-CoV-2 and subsequently COVID-19 severity. Second, at the boundary between the S1 and S2 subunits, it contains an insertion of four amino acids, which introduces a new furin cleavage site, which is likely to help in the processing of S protein at the S1 and S2 subunit boundary by ubiquitously expressed furin-like proteases for preliminary activation [63].

After binding, the S protein is proteolytically broken down at the boundary between the S1 and S2 subunits by

transmembrane protease serine 2 (TMPRSS2) which is present close to ACE2 in a process known as S protein priming; and thereafter increasing the membrane fusion with the host cell and subsequently the release of the viral genome into the host cells [64]. Other proteases such as factor Xa, trypsin and plasmin may also participate in this process [65].

Also; SARS-CoV-2 can enter the host cell by endocytosis. In this process; the S protein is activated in endosomes by the action of furin and cathepsin B/L (CatB/L) in endo-lysosomes [62], which finally triggers the fusion of viral envelope with the host cell membrane and then the release of viral RNA. It seems that the endosomal entry pathway might be the dominant coronavirus entry pathway in the infection of cells cultured in vitro, but its importance for infection in vivo remains unclear [66].

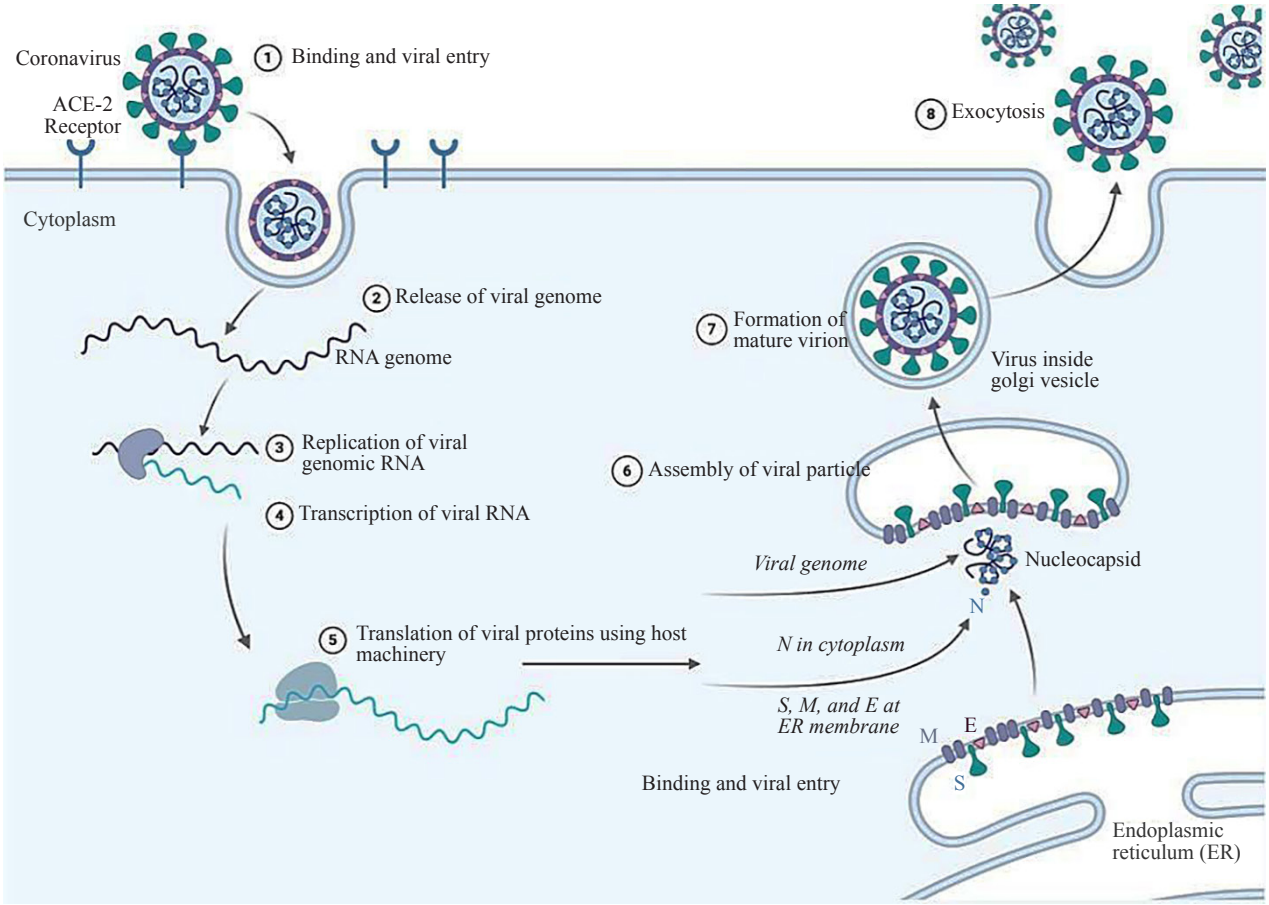


Figure 4. The Life cycle of SARS-CoV-2 in host cells. Firstly, SARS-CoV-2 enters target cells through an endosomal pathway, as viral S protein binds to the cellular receptor angiotensin-converting enzyme 2 (ACE2), and the ACE2-virus complex is then translocated to endosomes, where S protein is cleaved by transmembrane protease serine 2 (TMPRSS2) or the endosomal acid proteases (cathepsin L) to activate its fusion activity. Subsequently, viral genomic RNA is released into the host cell, and viral +ssRNA is translated into viral polymerase encoded by the genome, which initiates replication of +ssRNA to -ssRNA and further produces a series of genomic and subgenomic mRNAs. These are translated into viral proteins, which are subsequently assembled with genomic RNA into virions in the endoplasmic reticulum (ER) and the ER-Golgi intermediate compartment (ERGIC) to form mature virions that are trafficked via Golgi vesicles out of the cell by exocytosis and a new cell cycle may begin.

1.4.2 *Translation of viral replication machinery*

After the entry and uncoating of the viral endosome in the host cell cytoplasm, the coronavirus replicative cycle begins with the translation of mRNA into two polyproteins (pp1a and pp1ab) which are proteolytically cleaved by two viral proteases 3CLpro and PLpro to produce 16 mature non-structural proteins (nsps) [26].

1.4.3 *Replication*

Among the translated non-structural proteins, nsp12 (RNA-dependent RNA polymerase i.e. RdRp) binds with other nsps to form a replication and transcription complex (RTC), which is embedded in the double-membrane vesicles (DMVs) and responsible for the viral genome replication and transcription [66].

1.4.4 *Translation of viral structure proteins*

The products of viral RNA are localized in the DMVs and then transferred to the cytosol by the molecular pore complex across the double membrane. Then, the structural S, E and M proteins are translated in the endoplasmic reticulum and then transported to the Golgi apparatus for the assembly of virion [26].

1.4.5 *Assembly:*

The viral RNA and N protein assemble into the nucleocapsid in the cytoplasm and then associate with other viral structural proteins (S, M and E) to produce new viruses [50].

1.4.6 *Release of new viruses*

Finally, the new viral particles are released through exocytosis, and therefore ready to infect other host cells, and it so on [67].

1.5 *Immunopathological responses to SARS-CoV-2 infection*

SARS-CoV-2 infection could result in the production of immunopathological responses can lead to severe tissue damage if not controlled. After the entry of SARS-CoV-2 into human cells, the viral RNAs are released and can act as pathogen-associated molecular patterns (PAMPs), which are recognized by pattern recognition receptors (PRRs) such as retinoic acid-inducible gene-I (RIG-I) type I receptors and toll-like receptors (TLR3, TLR7 and TLR9). The binding of viral RNA to these receptors activates the translocation of different nuclear transcription factors as AP-1and NF-κB to the nucleus, which in turn increases the gene expression of acute inflammatory response proteins (C-CRP and SAA), pro-inflammatory cytokines and chemokines (IFNs, TNF-α, MPC-1, IP-10, IL-1, IL-6 and IL-8) [68-69]. The major antigen presentation cells (APCs) involved in the binding, processing and presentation of viral peptides are the dendritic cells, which are associated with class I and class II major histocompatibility complex (MHC) molecules for killer (CD8+) and helper (CD4+) T cells, respectively [70].

It is reported that severe COVID-19 patients have lymphopenia with a significant decrease in the B cells, NK cells, CD4+ T cells and CD8+ T cells, along with a reduced number of eosinophils, monocytes and basophils. In addition to this, the cytokines storm and chemokines such as TNF-α, MCP1, MIP1b, PDGFB, IL1-b, IL1Ra, IL6, IL7, IL8, IL9, IL10, Fibroblast growth factor 2, GCSF, GMCSF, IFNc, IP10, and VEGFA were found to be significantly increased in the COVID-19 patients [71-72]; which subsequently resulting in acute respiratory distress syndrome (ARDS), multiple organ failure and eventually death in the extreme cases of SARS-CoV-2 infection [69].

1.6 *Symptoms of SARS-CoV-2 infection*

Patients with COVID-19 can be either asymptomatic carriers or may have symptoms, ranging from fever, myalgia, dyspnea, dry cough and fatigue to severe respiratory infection or multiple organ dysfunction. Also; diarrhea, anosmia, abdominal pain, headache, dizziness, confusion, and hemoptysis may occur [73-74]. The incubation period of SARS-CoV-2 infection is 2-14 days; while in asymptomatic COVID-19 patients, it may be increased to 19 days [75-76]. The risk factors of SARS-CoV-2 infection are male gender, elder persons and patients with fundamental diseases such as diabetes mellitus, hypertension, chronic cardiac or kidney disease, and cancer [7].

According to the symptoms, COVID-19 disease can be classified into mild, moderate, severe, and critical. There are about 80% of COVID-19 patients with asymptomatic or mild infection, 15% with a serious illness requiring hospitalization, and 5% have critical life-threatening diseases such as cardiac and respiratory failures, septic shock, and

multiple organ dysfunctions [77].

1.7 *Complications of SARS-CoV-2 infection*

Several studies reported that COVID-19 affects mainly the respiratory system and also different organs [7-10]. The complications of SARS-CoV-2 infection can be divided into pulmonary and extra-pulmonary complications.

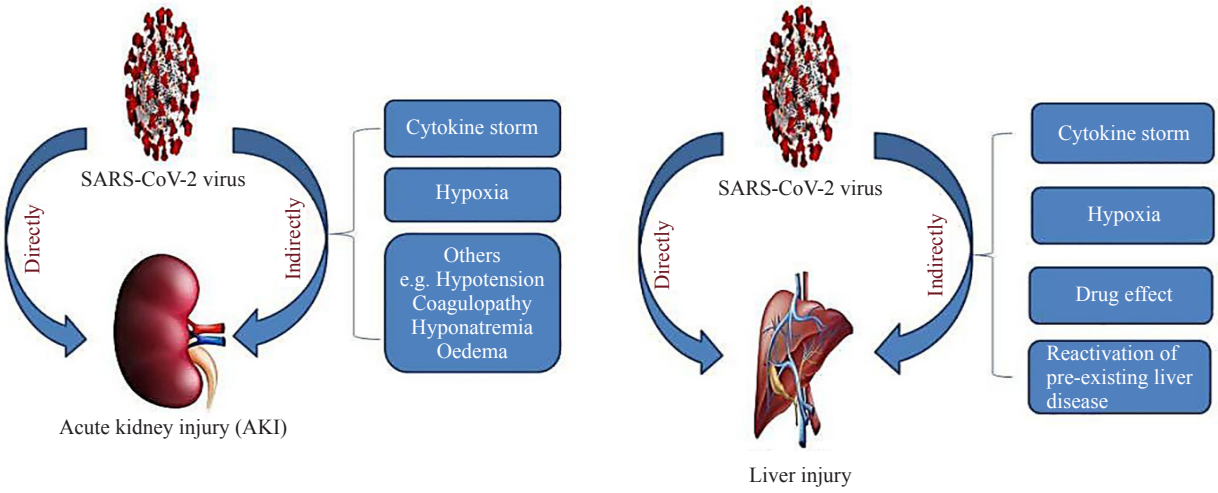
1.7.1 *Pulmonary complications of SARS-CoV-2 infection*

Lungs are the principal organs affected in the early stages of COVID-19 and the respiratory system is the front-line of the SARS-CoV-2 infection. The virus binds the ACE2 receptor, which is present mainly in the lower respiratory tract, and causes injury to the lungs in three ways: acute respiratory distress syndrome (ARDS) with diffuse alveolar damage (DAD), diffuse thrombotic alveolar microvascular occlusion, and inflammatory mediator-associated airway inflammation [78]. These combined actions cause impaired alveolar oxygenation, hypoxemia, and acidosis. Of the lack of effective treatment, the consequences of this poor oxygenation are either the death of the patient from respiratory failure or the sequelae of permanent lung injury if the patient recovers [78-79]. As a result, the typical pathophysiological feature of COVID-19 pneumonia/ARDS is that alveolar gas exchange and oxygenation are severely impaired [80]. Approximately one-third of COVID-19 survivors had significant pulmonary fibrosis [81].

The radiological evaluations and assessments such as chest CT imaging are critical for the detection and prognosis of SARS-CoV-2 infection as the X-ray chest radiography is not sensitive for the detection of ground-glass opacity, and may display normal results in the initial stage of SARS-CoV-2 infection [82]. The chest CT scan of COVID-19 patients shows different patterns, ranging from single ground-glass opacity (GGO) to bilateral diffuse heterogeneous consolidation with air bronchogram and bronchiectasis. COVID-19 patients with ARDS have higher mortality rates and neutrophilia, age, elevated LDH, and D-dimer are identified as risk factors for the development of ARDS [83].

1.7.2 *Extra-pulmonary complications of SARS-CoV-2 infection:*

Although lung infection and acute respiratory syndrome are the main features of SARS-CoV-2 infection, other organs such as the kidneys, liver, heart, small intestines, and brain are also present and the majority is the renal injury; as shown in Figure 5 [84]. Extra-pulmonary complications of SARS-CoV-2 infection include:



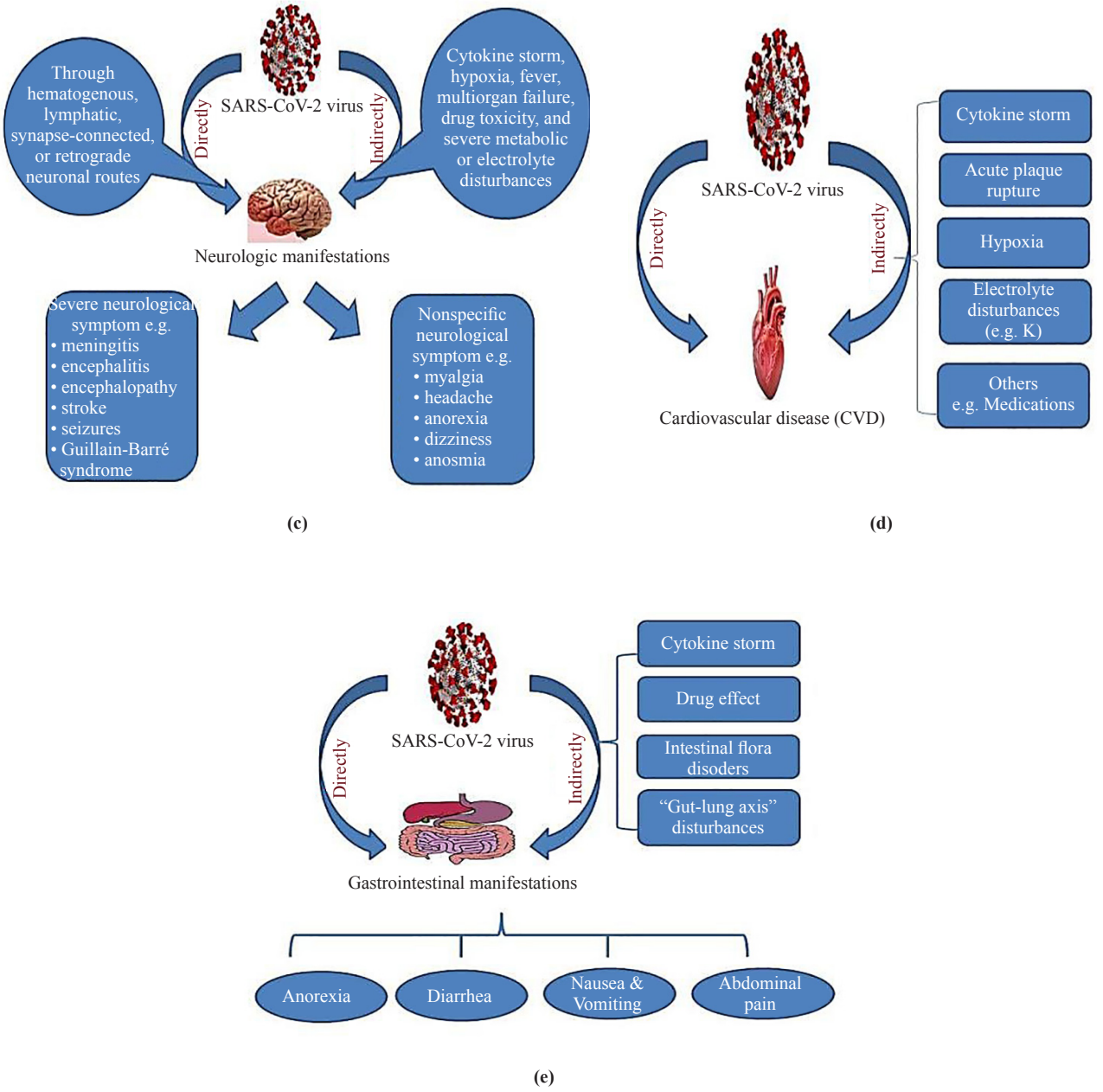


Figure 5. Possible causes of extra-pulmonary complications of SARS-CoV-2 infection. (a): Possible causes of acute kidney injury (AKI) in SARS-CoV-2 infection; (b): Possible causes of Liver injury in SARS-CoV-2 infection; (c): Neurological manifestations of SARS-CoV-2 infection; (d): Possible causes of cardiovascular disease (CVD) in SARS-CoV-2 infection; and (e): Gastrointestinal (GI) disturbance causes and manifestations in SARS-CoV-2 infection

1.7.2.1 *Renal Complications:*

Several studies reported the presence of renal functional impairment in COVID-19 patients [8, 85-86]. COVID-19 patients, especially critical patients, are at higher risk of developing acute kidney injury (AKI), which was reported to be a risk factor for mortality [87]. It was reported that AKI develops in about 0.5-7% of COVID-19 patients and this proportion raised to 2.9-23% in COVID-19 critically ill patients [7, 71, 88]. In China; there is a centric prospective cohort study including 701 COVID-19 patients who reported that there were 43.9% of patients with proteinuria 26.7% with hematuria on admission and 5.1% developed AKI during hospitalization [85]. Elevated BUN (14.3%), elevated

serum creatinine (10.7%) and albuminuria (38.8%) were also reported in COVID-19 patients.

It was believed that renal damage in COVID-19 patients was caused by directly SARS-CoV-2 infection or indirectly by virus-induced cytokines such as TNF-α, IL-6, and IL-10 [89]. Previous studies revealed that SARS-CoV-2 nucleocapsid protein is present in epithelial cells of the renal tubular [90-91], while other studies found that ACE-2 receptor and TMPRSS genes are expressed in the epithelial cells of kidneys such as in lungs, therefore; kidneys can be considered as an important target organ for SARS-CoV-2 infection [92]. These results suggest that AKI can be caused by SARS-CoV-2 either directly through cytopathic effect on kidney cells by binding to ACE-2 [93] which could clarify the presence of proteinuria and hematuria reported in a high percentage of COVID-19 patients [85] or indirectly through the pathological immune responses triggered by cellular damage; as shown in Figure 5(a).

1.7.2.2 *Hepatic complications*

Abnormal liver function has been reported in 16.1-66.6% of COVID-19 patients in several studies; that manifested by increased alanine transaminase to aspartate transaminase ratio (ALT/AST) along with decreased albumin concentration, slightly increased bilirubin level, and variable levels of alkaline phosphatase and gamma-glutamyl transferase (GGT) [7, 71, 88, 94]. The prevalence of liver impairment in severe COVID-19 patients was significantly increased when compared with mild patients [71, 94]. The proportion of liver impairment might reach 78% in nonsurvival COVID-19 patients. Previous studies revealed that the levels of ALT and AST in serum increased up to 7590 U/L and 1445 U/L, respectively; in a severe COVID-19 patient [95].

To date, studies on the mechanismatic procedure of liver damage by SARS-CoV-2 infection are limited. Several studies found that both hepatocytes (liver cells) and cholangiocytes (bile duct cells) express ACE2, but the expression of ACE2 in cholangiocytes is much higher than that of hepatocytes and similar to alveolar type 2 cells in the lung [96]. Therefore, it was suggested that cholangiocytes rather than hepatocytes were infected by SARS-CoV-2; which is explained by the presence of the virus in feces [97]. In the SARS-CoV pandemic, there is no proof of the presence of visible coronavirus particles in liver tissue by using TEM examination [98]. However, for SARS-CoV-2, there is a study reported the presence of SARS-CoV-2 viral particles in the hepatocytes cytoplasm of two COVID-19 patients and most of the viral particles were with entire envelope structure suggesting that SARS-CoV-2 not only enter but also replicate in the hepatocytes. This observation was proved by the different structural features of the impaired cell membrane, mitochondrial swelling, and dilatation of the endoplasmic reticulum. The immunohistochemistry results of the same study showed decreased levels of CD8+ and CD4+ T cells in liver tissues, indicating that immunopathologic harm might not be preferable in liver damage [99]. From several studies, there are five possible mechanisms of liver damage caused by SARS-CoV-2 infection, as shown in Figure 5(b):

1- Direct cytopathic effect is caused by the viral replication in hepatocytes and cholangiocytes [88, 96].

2- The enormous cytokines released from the immune system, i.e. cytokine storm, due to the viral infection; which can cause death in about 30% of died COVID-19 cases [100].

3- Drug-induced liver damage due to the use of hepatotoxic treatments like tocilizumab, ritonavir, remdesivir, tocilizumab, chloroquine, and uminefovir [101].

4- Liver damage due to hypoxia-i.e. an imbalance between organ oxygen supply and demand-as respiratory failure is one of the main characteristics of COVID-19 and patients with severe COVID-19 may develop hypoxic-ischemic liver injury [99, 102].

5- Pre-existing liver diseases can be reactivated due to SARS-CoV-2 infection [103].

1.7.2.3 *Neurological complications*

There is clinical evidence of neurological complications of SARS-CoV-2 infection as several reports revealed that the infection of SARS-CoV-2 may result in neurological complications in COVID-19 patients [104-105], especially in hospitalized severe patients [106]. The prevalence of neurological complications is about 37% in COVID-19 patients [106-108] and this proportion is increased to 88% in severe patients [106]. It is known that the ACE2 receptor is expressed in the neural tissue (glial cells and neurons), endothelial cells, and brain which makes them good targets for SARS-CoV-2 infection [109]. Also; the viral RNA was found in both brain tissue and cerebrospinal fluid of COVID-19 patients [110]. These findings emphasize the neurological damage of SARS-CoV-2 which can enter into the central

nervous system (CNS) either by hematogenous, lymphatic, synapse-connected, or retrograde neuronal routes [107, 110]. Neurological manifestations are generally observed in COVID-19 patients, and these might involve CNS, peripheral nervous system (PNS), and skeletal muscles [111]. In mild COVID-19 patients; numerous non-specific neurological manifestations are observable, including anorexia (40%), myalgia and/or fatigue (11-44%), headache (8-42%), dizziness (12%), anosmia (5%), and ageusia (5%) [7, 71, 95].

In COVID-19 patients, the most common nonspecific neurological symptom is myalgia. Cytokine storm and the resulting inflammation could be the main causes of myalgia [112]. Till now, it is still obscure whether muscle symptoms of COVID-19 are due to direct muscle invasion or an unspecific systemic inflammation. In severe COVID-19 patients, serum levels of lactate dehydrogenase (LDH) and creatine kinase (CK) can be significantly increased [113].

Several studies have reported that headache is the most common nonspecific neurological manifestation and is considered the fifth most frequent symptom of COVID-19 after fever, cough, myalgia/fatigue, and dyspnea [71, 114].

Olfactory and gustatory disorders are the most common sudden neurological manifestations of SARS-CoV-2 infection, which is associated with PNS involvement and seem to appear in the early stages of COVID-19 disease therefore it is believed to be diagnostic markers [115]. Previous studies revealed ACE2 receptor cannot be expressed by olfactory sensory neurons; therefore SARS-CoV-2 cannot infect these cells. While the olfactory epithelium cells express ACE2 and therefore are suitable for SARS-CoV-2 infection [116-117]. From these findings, we can conclude that the cause of anosmia associated with COVID-19 is due to SARS-CoV-2 damage to the olfactory epithelium rather than neuronal injury.

Also, neuralgia, hyposmia and hypogeusia were observed in some COVID-19 patients (2-10%). It was believed that SARS-CoV-2 passes to the CNS through the olfactory bulb as the epithelial cells of the nasal and oral cavity express high levels of ACE2 receptors therefore impairing the function of sensory neurons [106].

In severe COVID-19 patients; the neurological manifestations deteriorate to be acute stroke [118], confusion or impaired consciousness [119], meningitis, encephalitis, and meningoencephalitis infection [120], seizures and epilepsy [121]. In addition, Guillain-Barré syndrome [122], hemorrhagic posterior reversible encephalopathy syndrome [123] and acute necrotizing encephalopathy [124] have also been reported in some patients; as shown in Figure 5(c).

1.7.2.4 *Cardiovascular complications*

The COVID-19 patients may have severe cardiovascular disease (CVD) and patients with CVD have a higher risk of death. Several studies reported different cardiovascular presentations of COVID-19 [125-126]. A high percentage of pre-existing CVD has been exist among COVID-19 patients, and associated with increased mortality [7, 71, 88]. Also, COVID-19 may enhance the occurrence of cardiovascular disorders [10, 127]. The prevalence of developing CVD in severe COVID-19 patients is myocardial injury (20-30%) [10, 127], biventricular cardiomyopathy (7-33%) [128-129] of hospitalized COVID-19 patients. Cardiac arrhythmias and isolated right ventricular failure with or without confirmed pulmonary embolism are also reported with a prevalence of 17% of inpatients with COVID-19 [130]; while atrial arrhythmias were more common among mechanical ventilated COVID-19 patients [131].

SARS-CoV-2 can either directly or indirectly damage the heart causing cardiovascular complications such as arrhythmias, venous thromboembolism, myocardial injury, cardiomyopathy, acute coronary syndromes (ACS), and cardiogenic shock [125, 132]. The pathophysiology underlying the cardiovascular manifestations in SARS-CoV-2 infection is multifactorial. Cells of cardiovascular tissue such as cardiac endothelial cells, fibroblasts, myocytes, and smooth-muscle can express high amounts of ACE2 receptors which make them vulnerable to direct viral injury [133]. In addition, myocarditis, which is associated with viral load, is an assumed cause of cardiac dysfunction. Also, it was found that SARS-CoV-2 was isolated from the myocardial tissue in a few autopsy studies [134], while other studies reported inflammatory infiltrates without evidence of the presence of SARS-CoV-2 in myocardial tissues [135]. The cytokine storm resulting from SARS-CoV-2 infection is another putative mechanism of myocardial injury [136]. According to Xiong et al. [137], there are six possible mechanisms of myocardial injury caused by SARS-CoV-2 infection; as shown in Figure 5(d):

1- Direct infection: SARS-CoV-2 can damage myocardial cells directly through ACE2 receptors.

2- Cytokine storm: SARS-CoV-2 infection result in elevated levels of pro- and anti-inflammatory cytokines, which in turn can cause multiple organs injury, including heart.

3- Acute plaque rupture: Systematic inflammation can result in elevated plaque sensitivity and may be rupture

causing acute coronary syndrome.

4- Hypoxia: As respiratory failure is one of the main characteristics of COVID-19 and therefore inadequate myocardial oxygen supply/demand, thus resulting in myocardial damage.

5- Potassium (K) and other electrolyte disturbances: SARS-CoV-2 interacts with ACE2 receptors, resulting in defects of renin-angiotensin system causing hypokalemia which in turn induces serious arrhythmias.

6- Others: Such as immunological agents, antiviral drugs and corticosteroids side effects.

1.7.2.5 *Gastrointestinal complications*

It is known that SARS-CoV-2 mostly infects the respiratory system causing pneumonia; although, it also can affect the gastrointestinal (GI) tract [138]. Diarrhea, anorexia, vomiting, nausea, and abdominal pain are the most reported GI manifestations in COVID-19 patients [139]. Also, acute pancreatitis, GI bleeding, and colitis have been observed [140]. It was found that nearly one-fifth of COVID-19 patients were recorded to have GI manifestations [141]. It was reported that about 70% of COVID-19 patients have viral RNA shedding by GIT which continued for about 10 weeks after the beginning of symptoms [142]. It was observed that there is no significant damage to the epithelial cells of the esophagus, stomach, and duodenum tissues, while the most lymphocyte infiltration was observed in the squamous epithelium of lamina propria of the stomach, duodenum, and rectum causing abdominal pain [143].

Anorexia is considered the most frequent GI manifestation in COVID-19 patients, and its prevalence is 12.2-50.2% [7, 144]. Diarrhea is also a frequently observed GI manifestation in patients with COVID-19 and is considered a big problem, that is due to it is potential for feco-oral transmission of SARS-CoV-2 infection and its prevalence is 2-50% [145-146]. In addition, vomiting and nausea have been also observed among patients with COVID-19, either as their only manifestations or combined with other GI manifestations, with a prevalence of 5.2-28% [145-147]. COVID-19 patients may have abdominal pain at presentation, however, it is less common when compared to diarrhea, anorexia, nausea, or vomiting, and its prevalence is 3.9 to 6.8% [142, 145]. As shown in Figure 5(e); the putative mechanisms resulted in the GI involvement in COVID-19 patients are:

• Direct cytopathic effect: SARS-CoV-2 enters GIT through ACE-2 resulting in malabsorption, activated enteric nervous system, and unbalanced intestinal secretion [142].

• Indirectly through immunopathological inflammatory responses [148].

• Drug-induced GIT damage [149].

• Intestinal flora disorders induced by SARS-CoV-2 infection [150].

• "Gut-lung axis" disturbances [151].

1.7.2.6 *Other complications*

It is known that the ACE2 receptor can be expressed in a considerable amount by the pancreatic cells; therefore pancreas is vulnerable to SARS-CoV-2 infection. Several studies reported that hyperglycemia and an increased risk of diabetic ketoacidosis are associated with COVID-19 disease. The prevalence of pancreatic injury is 1-2% in mild COVID-19 patients, while this proportion is increasing to 17% in severe COVID-19 patients [152-153]. Also, it was found that COVID-19 is related to coagulopathy which was confirmed by the presence of thrombosis in pulmonary vessels, high levels of serum D-dimer, and disseminated intravascular coagulation (DIC) in severe COVID-19 patients [154-155]. Electrolyte imbalances, including decreased serum levels of potassium, sodium, and calcium, have been reported in severe COVID-19 patients [156]. Furthermore, cutaneous involvements in COVID-19 patients include urticarial, erythematous rash, and chickenpox-like vesicles [157-158]. Finally, eyelid edema and conjunctival hyperemia have been reported as initial manifestations of COVID-19 and about 2-32% of COVID-19 patients have ocular symptoms [159].

2. Conclusion

This review tried to discuss the history and classification of coronaviruses, geographical distribution of COVID-19, SARS-CoV-2 structure and genomic organization, life cycle, Immunopathological responses, symptoms, and finally

pulmonary and extra-pulmonary complications of SARS-CoV-2 infection. Understanding how SARS-CoV-2 can infect humans is critical for our understanding and prevention of future outbreaks of not only COVID-19 but also, other potential diseases, therefore future epidemiological studies are needed to further investigate the risk factors associated with adverse outcomes in patients with COVID-19 and monitor the long-term health impact.

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References

[1] Carty M, Guy C, Bowie AG. Detection of viral infections by innate immunity. *Biochemical Pharmacology*. 2021; 183: 114316.

[2] Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, et al. China novel coronavirus investigating and research team. A novel coronavirus from patients with pneumonia in China, 2019. *New England Journal of Medicine*. 2020; 382(8): 727-733.

[3] WHO. *Director-General's opening remarks at the media briefing on COVID-19-11 March 2020*. World Health Organization; 2020. Available from: https://www.who.int/dg/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19---11-march-2020.

[4] Abenavoli L, Cinaglia P, Luzza F, Gentile I, Boccuto L. Epidemiology of coronavirus disease outbreak: The italian trends. *Reviews in Recent Clinical Trials*. 2020; 15(2): 87-92.

[5] Worldometer. *COVID-19 Coronavirus Pandemic*. 2023. Available from: https://www.worldometers.info/coronavirus/ [Accessed 1th January 2022].

[6] Widiasta A, Sribudiani Y, Nugrahapraja H, Hilmanto D, Sekarwana N, Rachmadi D. Potential role of ACE2-related microRNAs in COVID-19-associated nephropathy. *Noncoding RNA Research*. 2020; 5(4): 153-166.

[7] Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in wuhan, China. *JAMA*. 2020; 323(11): 1061-1069.

[8] Raza A, Estepa A, Chan V, Jafar MS. Acute renal failure in critically Ill COVID-19 patients with a focus on the role of renal replacement therapy: A review of what we know so far. *Cureus*. 2020; 12(6): e8429.

[9] Becker RC. COVID-19 update: Covid-19-associated coagulopathy. *Journal of Thrombosis and Thrombolysis*. 2020; 50(1): 54-67.

[10] Shi S, Qin M, Shen B, Cai Y, Liu T, Yang F, et al. Association of cardiac injury with mortality in hospitalized patients with COVID-19 in Wuhan, China. *JAMA Cardiology*. 2020; 5(7): 802-810.

[11] Schalk A, Hawn MC. An apparently new respiratory disease of baby chicks. *Journal of the American Veterinary Medical Association*. 1931; 78: 413-423.

[12] Tyrrell DA, Bynoe ML. Cultivation of viruses from a high proportion of patients with colds. *Lancet*. 1966; 1(7428): 76-77.

[13] Tyrrell DAJ, Almeida JD, Berry DM, Cunningham CH, Hamre D, Hofstad MS, et al. Coronaviruses. *Nature*. 1968; 220: 650.

[14] Weiss SR, Navas-Martin S. Coronavirus pathogenesis and the emerging pathogen severe acute respiratory

syndrome coronavirus. *Microbiology and Molecular Biology Reviews*. 2005; 69(4): 635-664.
[15] Woo PC, Lau SK, Lam CS, Lau CC, Tsang AK, Lau JH, et al. Discovery of seven novel Mammalian and avian coronaviruses in the genus deltacoronavirus supports bat coronaviruses as the gene source of alphacoronavirus and betacoronavirus and avian coronaviruses as the gene source of gammacoronavirus and deltacoronavirus. *Journal of Virology*. 2012; 86(7): 3995-4008.
[16] Tang Q, Song Y, Shi M, Cheng Y, Zhang W, Xia XQ. Inferring the hosts of coronavirus using dual statistical models based on nucleotide composition. *Scientific Reports*. 2015; 5: 17155.
[17] Snijder EJ, Bredenbeek PJ, Dobbe JC, Thiel V, Ziebuhr J, Poon LL, et al. Unique and conserved features of genome and proteome of SARS-coronavirus, an early split-off from the coronavirus group 2 lineage. *Journal of Molecular Biology*. 2003; 331(5): 991-1004.
[18] Chan JF, Lau SK, To KK, Cheng VC, Woo PC, Yuen KY. Middle east respiratory syndrome coronavirus: Another zoonotic betacoronavirus causing SARS-like disease. *Clinical Microbiology Reviews*. 2015; 28(2): 465-522.
[19] Woo PC, Huang Y, Lau SK, Yuen KY. Coronavirus genomics and bioinformatics analysis. *Viruses*. 2010; 2(8): 1804-1820.
[20] Liu DX, Liang JQ, Fung TS. Human coronavirus-229E, -OC43, -NL63, and -HKU1 (coronaviridae). *Encyclopedia of Virology*. 2021; 428-440.
[21] Peiris JS, Yuen KY, Osterhaus AD, Stöhr K. The severe acute respiratory syndrome. *New England Journal of Medicine*. 2003; 349(25): 2431-2441.
[22] WHO. *Middle East respiratory syndrome coronavirus (MERS-CoV)*. 2023. Available from: https://www.who.int/emergencies/mers-cov/en/ [Accessed 29th February 2020].
[23] Wang MY, Zhao R, Gao LJ, Gao XF, Wang DP, Cao JM. SARS-CoV-2: Structure, biology, and structure-based therapeutics development. *Frontiers in Cellular and Infection Microbiology*. 2020; 10: 587269.
[24] Zhou P, Yang XL, Wang XG, Hu B, Zhang L, Zhang W, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. *Nature*. 2020; 579(7798): 270-273.
[25] Jungreis I, Sealfon R, Kellis M. SARS-CoV-2 gene content and COVID-19 mutation impact by comparing 44 Sarbecovirus genomes. *Nature Communications*. 2021; 12(1): 2642.
[26] Wu F, Zhao S, Yu B, Chen YM, Wang W, Song ZG, et al. A new coronavirus associated with human respiratory disease in China. *Nature*. 2020; 579(7798): 265-269.
[27] Mousavizadeh L, Ghasemi S. Genotype and phenotype of COVID-19: Their roles in pathogenesis. *Journal of Microbiology, Immunology, and Infection*. 2021; 54(2): 159-163.
[28] Wang C, Liu Z, Chen Z, Huang X, Xu M, He T, et al. The establishment of reference sequence for SARS-CoV-2 and variation analysis. *Journal of Medical Virology*. 2020; 92(6): 667-674.
[29] Liu DX, Fung TS, Chong KK, Shukla A, Hilgenfeld R. Accessory proteins of SARS-CoV and other coronaviruses. *Antiviral Research*. 2014; 109: 97-109.
[30] Chan JF, Kok KH, Zhu Z, Chu H, To KK, Yuan S, et al. Genomic characterization of the 2019 novel human-pathogenic coronavirus isolated from a patient with atypical pneumonia after visiting Wuhan. *Emerging Microbes & Infections*. 2020; 9(1): 221-236.
[31] Züst R, Cervantes-Barragán L, Kuri T, Blakqori G, Weber F, Ludewig B, et al. Coronavirus non-structural protein 1 is a major pathogenicity factor: implications for the rational design of coronavirus vaccines. *PLoS Pathogens*. 2007; 3(8): e109.
[32] Kamitani W, Huang C, Narayanan K, Lokugamage KG, Makino S. A two-pronged strategy to suppress host protein synthesis by SARS coronavirus Nsp1 protein. *Nature Structural & Molecular Biology*. 2009; 16(11): 1134-1140.
[33] Cornillez-Ty CT, Liao L, Yates JR, Kuhn P, Buchmeier MJ. Severe acute respiratory syndrome coronavirus nonstructural protein 2 interacts with a host protein complex involved in mitochondrial biogenesis and intracellular signaling. *Journal of Virology*. 2009; 83(19): 10314-10318.
[34] Neuman BW, Joseph JS, Saikatendu KS, Serrano P, Chatterjee A, Johnson MA, et al. Proteomics analysis unravels the functional repertoire of coronavirus nonstructural protein 3. *Journal of Virology*. 2008; 82(11): 5279-5294.
[35] Lei J, Kusov Y, Hilgenfeld R. Nsp3 of coronaviruses: Structures and functions of a large multi-domain protein. *Antiviral Research*. 2018; 149: 58-74.
[36] Manolaridis I, Wojdyla JA, Panjikar S, Snijder EJ, Gorbalenya AE, Berglind H, et al. Structure of the C-terminal domain of nsp4 from feline coronavirus. *Acta Crystallographica Section D Biological Crystallography*. 2009; 65(8): 839-846.
[37] Anand K, Ziebuhr J, Wadhwani P, Mesters JR, Hilgenfeld R. Coronavirus main proteinase (3CLpro) structure: Basis for design of anti-SARS drugs. *Science*. 2003; 300(5626): 1763-1767.
[38] Cottam EM, Whelband MC, Wileman T. Coronavirus NSP6 restricts autophagosome expansion. *Autophagy*. 2014;

10(8): 1426-1441.
[39] Oostra M, Hagemeijer MC, van Gent M, Bekker CP, te Lintelo EG, Rottier PJ, et al. Topology and membrane anchoring of the coronavirus replication complex: Not all hydrophobic domains of nsp3 and nsp6 are membrane-spanning. *Journal of Virology*. 2008; 82(24): 12392-12405.
[40] Zhai Y, Sun F, Li X, Pang H, Xu X, Bartlam M, et al. Insights into SARS-CoV transcription and replication from the structure of the nsp7-nsp8 hexadecamer. *Nature Structural & Molecular Biology*. 2005; 12(11): 980-986.
[41] Egloff MP, Ferron F, Campanacci V, Longhi S, Rancurel C, Dutartre H, et al. The severe acute respiratory syndrome-coronavirus replicative protein nsp9 is a single-stranded RNA-binding subunit unique in the RNA virus world. *Proceedings of the National Academy of Sciences of the United States of America*. 2004; 101(11): 3792-3796.
[42] Decroly E, Debarnot C, Ferron F, Bouvet M, Coutard B, Imbert I, et al. Crystal structure and functional analysis of the SARS-coronavirus RNA cap 2'-O-methyltransferase nsp10/nsp16 complex. *PLoS Pathogens*. 2011; 7(5): e1002059.
[43] Kirchdoerfer RN, Ward AB. Structure of the SARS-CoV nsp12 polymerase bound to nsp7 and nsp8 co-factors. *Nature Communications*. 2019; 10(1): 2342.
[44] Ivanov KA, Ziebuhr J. Human coronavirus 229E nonstructural protein 13: characterization of duplex-unwinding, nucleoside triphosphatase, and RNA 5'-triphosphatase activities. *Journal of Virology*. 2004; 78(14): 7833-7838.
[45] Eckerle LD, Lu X, Sperry SM, Choi L, Denison MR. High fidelity of murine hepatitis virus replication is decreased in nsp14 exoribonuclease mutants. *Journal of Virology*. 2007; 81(22): 12135-12144.
[46] Chen Y, Cai H, Pan J, Xiang N, Tien P, Ahola T, et al. Functional screen reveals SARS coronavirus nonstructural protein nsp14 as a novel cap N7 methyltransferase. *Proceedings of the National Academy of Sciences of the United States of America*. 2009; 106(9): 3484-3489.
[47] Kindler E, Gil-Cruz C, Spanier J, Li Y, Wilhelm J, Rabouw HH, et al. Early endonuclease-mediated evasion of RNA sensing ensures efficient coronavirus replication. *PLoS Pathogens*. 2017; 13(2): e1006195.
[48] Menachery VD, Debbink K, Baric RS. Coronavirus non-structural protein 16: evasion, attenuation, and possible treatments. *Virus Research*. 2014; 194: 191-199.
[49] Decroly E, Imbert I, Coutard B, Bouvet M, Selisko B, Alvarez K, et al. Coronavirus nonstructural protein 16 is a cap-0 binding enzyme possessing (nucleoside-2'O)-methyltransferase activity. *Journal of Virology*. 2008; 82(16): 8071-8084.
[50] Ren Y, Shu T, Wu D, Mu J, Wang C, Huang M, et al. The ORF3a protein of SARS-CoV-2 induces apoptosis in cells. *Cellular and Molecular Immunology*. 2020; 17(8): 881-883.
[51] Freundt EC, Yu L, Park E, Lenardo MJ, Xu XN. Molecular determinants for subcellular localization of the severe acute respiratory syndrome coronavirus open reading frame 3b protein. *Journal of Virology*. 2009; 83(13): 6631-6640.
[52] Kopecky-Bromberg SA, Martínez-Sobrido L, Frieman M, Baric RA, Palese P. Severe acute respiratory syndrome coronavirus open reading frame (ORF) 3b, ORF 6, and nucleocapsid proteins function as interferon antagonists. *Journal of Virology*. 2007; 81(2): 548-557.
[53] Gunalan V, Mirazimi A, Tan YJ. A putative acidic motif in the SARS-CoV ORF6 protein influences its subcellular localization and suppression of expression of co-transfected expression constructs. *BMC Research Notes*. 2011; 4: 446.
[54] Morante S, La Penna G, Rossi G, Stellato F. SARS-CoV-2 Virion Stabilization by Zn Binding. *Frontiers in Molecular Biosciences*. 2020; 7: 222.
[55] Schaecher SR, Mackenzie JM, Pekosz A. The ORF7b protein of severe acute respiratory syndrome coronavirus (SARS-CoV) is expressed in virus-infected cells and incorporated into SARS-CoV particles. *Journal of Virology*. 2007; 81(2): 718-731.
[56] Zhang Y, Zhang J, Chen Y, Luo B, Yuan Y, Huang F, et al. *The ORF8 Protein of SARS-CoV-2 Mediates Immune Evasion through Potently Downregulating MHC-I*. bioRxiv; 2020. Available from: doi:10.1101/2020.05.24.111823.
[57] Jiang HW, Zhang HN, Meng QF, Xie J, Li Y, Chen H, et al. SARS-CoV-2 Orf9b suppresses type I interferon responses by targeting TOM70. *Cellular and Molecular Immunology*. 2020; 17(9): 998-1000.
[58] Bojkova D, Klann K, Koch B, Widera M, Krause D, Ciesek S, et al. Proteomics of SARS-CoV-2-infected host cells reveals therapy targets. *Nature*. 2020; 583(7816): 469-472.
[59] Baruah C, Devi P, Sharma DK. Sequence analysis and structure prediction of SARS-CoV-2 accessory proteins 9b and ORF14: Evolutionary analysis indicates close relatedness to bat coronavirus. *Biomedical Research International*. 2020; 2020: 7234961.
[60] Wrapp D, Wang N, Corbett KS, Goldsmith JA, Hsieh CL, Abiona O, et al. Cryo-EM structure of the 2019-nCoV

spike in the prefusion conformation. *Science*. 2020; 367(6483): 1260-1263.
[61] Walls AC, Park YJ, Tortorici MA, Wall A, McGuire AT, Veesler D. Structure, function, and antigenicity of the SARS-CoV-2 spike glycoprotein. *Cell*. 2020; 181(2): 281-292.
[62] Hoffmann M, Kleine-Weber H, Schroeder S, Krüger N, Herrler T, Erichsen S, et al. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. *Cell*. 2020; 181(2): 271-280.
[63] Nishiga M, Wang DW, Han Y, Lewis DB, Wu JC. COVID-19 and cardiovascular disease: from basic mechanisms to clinical perspectives. *Nature Reviews Cardiology*. 2020; 17(9): 543-558.
[64] Bestle D, Heindl MR, Limburg H, Van Lam van T, Pilgram O, Moulton H, et al. TMPRSS2 and furin are both essential for proteolytic activation of SARS-CoV-2 in human airway cells. *Life Science Alliance*. 2020; 3(9): e202000786.
[65] Hoffmann M, Kleine-Weber H, Pöhlmann S. A multibasic cleavage site in the spike protein of SARS-CoV-2 is essential for infection of human lung cells. *Molecular Cell*. 2020; 78(4): 779-784.
[66] Wang Q, Wu J, Wang H, Gao Y, Liu Q, Mu A, et al. Structural basis for RNA replication by the SARS-CoV-2 polymerase. *Cell*. 2020; 182(2): 417-428.
[67] Buratta S, Tancini B, Sagini K, Delo F, Chiaradia E, Urbanelli L, et al. Lysosomal exocytosis, exosome release and secretory autophagy: the autophagic- and endo-lysosomal systems go extracellular. *International Journal of Molecular Sciences*. 2020; 21(7): 2576.
[68] Portela Sousa C, Brites C. Immune response in SARS-CoV-2 infection: The role of interferons type I and type III. *Brazilian Journal of Infectious Diseases*. 2020; 24(5): 428-433.
[69] Khade SM, Yabaji SM, Srivastava J. An update on COVID-19: SARS-CoV-2 life cycle, immunopathology, and BCG vaccination. *Preparative Biochemistry & Biotechnology*. 2021; 51(7): 650-658. Available from: doi:10.1080/10826068.2020.1848869.
[70] Le Bon A, Etchart N, Rossmann C, Ashton M, Hou S, Gewert D, et al. Cross-priming of CD8+ T cells stimulated by virus-induced type I interferon. *Nature Immunology*. 2003; 4(10): 1009-1015.
[71] Haroun RA, Osman WH, Amin RE, Eessa AM, Saad S. Increased serum interleukin-6 and lactate dehydrogenase levels among nonsurvival severe COVID-19 patients when compared to survival ones. *International Immunopharmacology*. 2023; 122: 110626.
[72] Haroun RA, Osman WH, Eessa AM. Interferon-γ-induced protein 10 (IP-10) and serum amyloid A (SAA) are excellent biomarkers for the prediction of COVID-19 progression and severity. *Life Sciences*. 2021; 269: 119019.
[73] Berlin DA, Gulick RM, Martinez FJ. Severe Covid-19. *New England Journal of Medicine*. 2020; 383(25): 2451-2460.
[74] Di Gennaro F, Pizzol D, Marotta C, Antunes M, Racalbuto V, Veronese N, et al. Coronavirus diseases (COVID-19) current status and future perspectives: A narrative review. *International Journal of Environmental Research and Public Health*. 2020; 17(8): 2690.
[75] Bai Y, Yao L, Wei T, Tian F, Jin DY, Chen L, et al. Presumed asymptomatic carrier transmission of COVID-19. *JAMA*. 2020; 323(14): 1406-1407.
[76] Li Q, Guan X, Wu P, Wang X, Zhou L, Tong Y, et al. Early transmission dynamics in wuhan, China, of novel coronavirus-infected pneumonia. *New England Journal of Medicine*. 2020; 382(13): 1199-1207.
[77] Baksh M, Ravat V, Zaidi A, Patel RS. A systematic review of cases of acute respiratory distress syndrome in the coronavirus disease 2019 pandemic. *Cureus*. 2020; 12(5): e8188.
[78] Calabrese F, Pezzuto F, Fortarezza F, Hofman P, Kern I, Panizo A, et al. Pulmonary pathology and COVID-19: lessons from the autopsy. The experience of European Pulmonary Pathologists. *Virchows Archiv*. 2020; 477(3): 359-372.
[79] Xu Z, Shi L, Wang Y, Zhang J, Huang L, Zhang C, et al. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. *Lancet Respiratory Medicine*. 2020; 8(4): 420-422.
[80] Shao C, Liu H, Meng L, Sun L, Wang Y, Yue Z, et al. Evolution of severe acute respiratory syndrome coronavirus 2 RNA test results in a patient with fatal coronavirus disease 2019: A case report. *Human Pathology*. 2020; 101: 82-88.
[81] Zhang P, Li J, Liu H, Han N, Ju J, Kou Y, et al. Long-term bone and lung consequences associated with hospital-acquired severe acute respiratory syndrome: A 15-year follow-up from a prospective cohort study. *Bone Research*. 2020; 8: 8.
[82] Ng MY, Lee EYP, Yang J, Yang F, Li X, Wang H, et al. Imaging profile of the COVID-19 infection: Radiologic findings and literature review. *Radiology Cardiothoracic Imaging*. 2020; 2(1): e200034.
[83] Wu C, Chen X, Cai Y, Xia J, Zhou X, Xu S, et al. Risk factors associated with acute respiratory distress syndrome

and death in patients with coronavirus disease 2019 pneumonia in wuhan, China. *JAMA Internal Medicine*. 2020; 180(7): 934-943.
[84] Hong XW, Chi ZP, Liu GY, Huang H, Guo SQ, Fan JR, et al. Characteristics of renal function in patients diagnosed with COVID-19: An observational study. *Frontiers in Medicine (Lausanne)*. 2020; 7: 409.
[85] Cheng Y, Luo R, Wang K, Zhang M, Wang Z, Dong L, et al. Kidney disease is associated with in-hospital death of patients with COVID-19. *Kidney International*. 2020; 97(5): 829-838.
[86] Pei G, Zhang Z, Peng J, Liu L, Zhang C, Yu C, et al. Renal involvement and early prognosis in patients with COVID-19 pneumonia. *Journal of the American Society of Nephrology*. 2020; 31(6): 1157-1165.
[87] Brienza N, Puntillo F, Romagnoli S, Tritapepe L. Acute kidney injury in coronavirus disease 2019 infected patients: A meta-analytic study. *Blood Purification*. 2021; 50(1): 35-41.
[88] Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, et al. China medical treatment expert group for covid-19. clinical characteristics of coronavirus disease 2019 in China. *New England Journal of Medicine*. 2020; 382(18): 1708-1720.
[89] Liu J, Zheng X, Tong Q, Li W, Wang B, Sutter K, et al. Overlapping and discrete aspects of the pathology and pathogenesis of the emerging human pathogenic coronaviruses SARS-CoV, MERS-CoV, and 2019-nCoV. *Journal of Medical Virology*. 2020; 92(5): 491-494.
[90] Diao B, Wang C, Wang R, Feng Z, Zhang J, Yang H, et al. Human kidney is a target for novel severe acute respiratory syndrome coronavirus 2 infection. *Nature Communications*. 2021; 12(1): 2506.
[91] Su H, Yang M, Wan C, Yi LX, Tang F, Zhu HY, et al. Renal histopathological analysis of 26 postmortem findings of patients with COVID-19 in China. *Kidney International*. 2020; 98(1): 219-227.
[92] Pan XW, Xu D, Zhang H, Zhou W, Wang LH, Cui XG. Identification of a potential mechanism of acute kidney injury during the COVID-19 outbreak: A study based on single-cell transcriptome analysis. *Intensive Care Medicine.* 2020; 46(6): 1114-1116.
[93] Batlle D, Soler MJ, Sparks MA, Hiremath S, South AM, Welling PA, et al. COVID-19 and ACE2 in Cardiovascular, Lung, and Kidney Working Group. Acute Kidney injury in COVID-19: Emerging evidence of a distinct pathophysiology. *Journal of the American Society of Nephrology*. 2020; 31(7): 1380-1383.
[94] Cai Q, Huang D, Ou P, Yu H, Zhu Z, Xia Z, et al. COVID-19 in a designated infectious diseases hospital outside Hubei Province, China. *Allergy*. 2020; 75(7): 1742-1752.
[95] Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: A descriptive study. *The Lancet*. 2020; 395(10223): 507-513.
[96] Xu L, Liu J, Lu M, Yang D, Zheng X. Liver injury during highly pathogenic human coronavirus infections. *Liver International*. 2020; 40(5): 998-1004.
[97] Boettler T, Newsome PN, Mondelli MU, Maticic M, Cordero E, Cornberg M, et al. Care of patients with liver disease during the COVID-19 pandemic: EASL-ESCMID position paper. *JHEP Reports*. 2020; 2(3): 100113.
[98] Chau TN, Lee KC, Yao H, Tsang TY, Chow TC, Yeung YC, et al. SARS-associated viral hepatitis caused by a novel coronavirus: report of three cases. *Hepatology*. 2004; 39(2): 302-310.
[99] Wang Y, Liu S, Liu H, Li W, Lin F, Jiang L, et al. SARS-CoV-2 infection of the liver directly contributes to hepatic impairment in patients with COVID-19. *Journal of Hepatology*. 2020; 73(4): 807-816.
[100]Chen G, Wu D, Guo W, Cao Y, Huang D, Wang H, et al. Clinical and immunological features of severe and moderate coronavirus disease 2019. *Journal of Clinical Investigation*. 2020; 130(5): 2620-2629.
[101]Food US. *Administration Drug*. Fact sheet for health care providers: Emergency Use Authorization (EUA) of hydroxychloroquine sulfate supplied from the strategic national stockpile for treatment of COVID-19 in certain hospitalized patients; 2020.
[102]Henrion J, Schapira M, Luwaert R, Colin L, Delannoy A, Heller FR. Hypoxic hepatitis: clinical and hemodynamic study in 142 consecutive cases. *Medicine (Baltimore)*. 2003; 82(6): 392-406.
[103]Varona Pérez J, Rodriguez Chinesta JM. Riesgo de reactivación de la hepatitis B asociado al tratamiento con corticoides frente a SARS-CoV-2 (COVID-19) [Risk of hepatitis B reactivation associated with treatment against SARS-CoV-2 (COVID-19) with corticosteroids]. *Rev Clin Esp*. 2020; 220(8): 534-536.
[104]Filatov A, Sharma P, Hindi F, Espinosa PS. Neurological complications of coronavirus disease (COVID-19): Encephalopathy. *Cureus*. 2020; 12(3): e7352.
[105]Zhou L, Zhang M, Wang J, Gao J. Sars-Cov-2: Underestimated damage to the nervous system. *Travel Medicine and Infectious Disease*. 2020; 36: 101642.
[106]Mao L, Jin H, Wang M, Hu Y, Chen S, He Q, et al. Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in wuhan, China. *JAMA Neurology*. 2020; 77(6): 683-690.
[107]Li YC, Bai WZ, Hashikawa T. The neuroinvasive potential of SARS-CoV2 may play a role in the respiratory

failure of COVID-19 patients. *Journal of Medical Virology*. 2020; 92(6): 552-555.
[108]Pleasure SJ, Green AJ, Josephson SA. The spectrum of neurologic disease in the severe acute respiratory syndrome coronavirus 2 pandemic infection: Neurologists move to the frontlines. *JAMA Neurology*. 2020; 77(6): 679-680.
[109]Baig AM, Khaleeq A, Ali U, Syeda H. Evidence of the COVID-19 virus targeting the CNS: Tissue distribution, host-virus interaction, and proposed neurotropic mechanisms. *ACS Chemical Neuroscience*. 2020; 11(7): 995-998.
[110]Marc D, Dominique JF, Brison É, Desjardins J, Meessen-Pinard M, Jacomy H, et al. *Human Coronavirus: Respiratory Pathogens Revisited as Infectious Neuroinvasive, Neurotropic, and Neurovirulent Agents*. CRC Press; Boca Raton, FL, USA; 2013. p.93-122.
[111]Asadi-Pooya AA, Simani L. Central nervous system manifestations of COVID-19: A systematic review. *Journal of the Neurological Sciences*. 2020; 413: 116832.
[112]Tsai ST, Lu MK, San S, Tsai CH. The neurologic manifestations of coronavirus disease 2019 pandemic: A systematic review. *Frontiers in Neurology*. 2020; 11: 498.
[113]Lippi G, Wong J, Henry BM. Myalgia may not be associated with severity of coronavirus disease 2019 (COVID-19). *World Journal of Emergency Medicine*. 2020; 11(3): 193-194.
[114]Borges do Nascimento IJ, Cacic N, Abdulazeem HM, von Groote TC, Jayarajah U, Weerasekara I, et al. Novel coronavirus infection (COVID-19) in humans: A scoping review and meta-analysis. *Journal of Clinical Medicine*. 2020; 9(4): 941.
[115]Cooper KW, Brann DH, Farruggia MC, Bhutani S, Pellegrino R, Tsukahara T, et al. COVID-19 and the chemical senses: Supporting players take center stage. *Neuron*. 2020; 107(2): 219-233.
[116]Brann DH, Tsukahara T, Weinreb C, Lipovsek M, Van den Berge K, Gong B, et al. Non-neuronal expression of SARS-CoV-2 entry genes in the olfactory system suggests mechanisms underlying COVID-19-associated anosmia. *Science Advances*. 2020; 6(31): eabc5801.
[117]Fodoulian L, Tuberosa J, Rossier D, Boillat M, Kan C, Pauli V, et al. SARS-CoV-2 receptors and entry genes are expressed in the human olfactory neuroepithelium and brain. *iScience*. 2020; 23(12): 101839.
[118]Oxley TJ, Mocco J, Majidi S, Kellner CP, Shoirah H, Singh IP, et al. Large-vessel stroke as a presenting feature of covid-19 in the young. *New England Journal of Medicine*. 2020; 382(20): e60.
[119]Pilotto A, Odolini S, Masciocchi S, Comelli A, Volonghi I, Gazzina S, et al. Steroid-responsive encephalitis in coronavirus disease 2019. *Annals of Neurology*. 2020; 88(2): 423-427.
[120]Duong L, Xu P, Liu A. Meningoencephalitis without respiratory failure in a young female patient with COVID-19 infection in Downtown Los Angeles, early April 2020. *Brain, Behavior, and Immunity*. 2020; 87: 33.
[121]Lyons S, O'Kelly B, Woods S, Rowan C, Brady D, Sheehan G, et al. Seizure with CSF lymphocytosis as a presenting feature of COVID-19 in an otherwise healthy young man. *Seizure*. 2020; 80: 113-114.
[122]Toscano G, Palmerini F, Ravaglia S, Ruiz L, Invernizzi P, Cuzzoni MG, et al. Guillain-barré syndrome associated with SARS-CoV-2. *New England Journal of Medicine*. 2020; 382(26): 2574-2576.
[123]Franceschi AM, Ahmed O, Giliberto L, Castillo M. Hemorrhagic posterior reversible encephalopathy syndrome as a manifestation of COVID-19 infection. *AJNR American Journal of Neuroradiology*. 2020; 41(7): 1173-1176.
[124]Poyiadji N, Shahin G, Noujaim D, Stone M, Patel S, Griffith B. COVID-19-associated acute hemorrhagic necrotizing encephalopathy: Imaging features. *Radiology*. 2020; 296(2): E119-E120.
[125]Clerkin KJ, Fried JA, Raikhelkar J, Sayer G, Griffin JM, Masoumi A, et al. COVID-19 and cardiovascular disease. *Circulation*. 2020; 141(20): 1648-1655.
[126]Zheng YY, Ma YT, Zhang JY, Xie X. COVID-19 and the cardiovascular system. *Nature Reviews Cardiology*. 2020; 17(5): 259-260.
[127]Guo T, Fan Y, Chen M, Wu X, Zhang L, He T, et al. Cardiovascular implications of fatal outcomes of patients with coronavirus disease 2019 (COVID-19). *JAMA Cardiology*. 2020; 5(7): 811-818.
[128]Ruan Q, Yang K, Wang W, Jiang L, Song J. Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. *Intensive Care Medicine*. 2020; 46(5): 846-848.
[129]Arentz M, Yim E, Klaff L, Lokhandwala S, Riedo FX, Chong M, et al. Characteristics and outcomes of 21 critically Ill patients with COVID-19 in Washington State. *JAMA*. 2020; 323(16): 1612-1614.
[130]Ullah W, Saeed R, Sarwar U, Patel R, Fischman DL. COVID-19 complicated by acute pulmonary embolism and right-sided heart failure. *JACC Case Reports*. 2020; 2(9): 1379-1382.
[131]Goyal P, Choi JJ, Pinheiro LC, Schenck EJ, Chen R, Jabri A, et al. Clinical characteristics of Covid-19 in New York city. *New England Journal of Medicine*. 2020; 382(24): 2372-2374.
[132]Driggin E, Madhavan MV, Bikdeli B, Chuich T, Laracy J, Biondi-Zoccai G, et al. Cardiovascular considerations for patients, health care workers, and health systems during the COVID-19 pandemic. *Journal of the American College of Cardiology*. 2020; 75(18): 2352-2371.

[133]Hamming I, Timens W, Bulthuis ML, Lely AT, Navis G, van Goor H. Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis. *Journal of Pathology*. 2004; 203(2): 631-637.
[134]Tavazzi G, Pellegrini C, Maurelli M, Belliato M, Sciutti F, Bottazzi A, et al. Myocardial localization of coronavirus in COVID-19 cardiogenic shock. *European Journal of Heart Failure*. 2020; 22(5): 911-915.
[135]Sala S, Peretto G, Gramegna M, Palmisano A, Villatore A, Vignale D, et al. Acute myocarditis presenting as a reverse Tako-Tsubo syndrome in a patient with SARS-CoV-2 respiratory infection. *European Heart Journal*. 2020; 41(19): 1861-1862.
[136]Li H, Liu L, Zhang D, Xu J, Dai H, Tang N, et al. SARS-CoV-2 and viral sepsis: Observations and hypotheses. *Lancet*. 2020; 395(10235): 1517-1520.
[137]Xiong TY, Redwood S, Prendergast B, Chen M. Coronaviruses and the cardiovascular system: Acute and long-term implications. *European Heart Journal*. 2020; 41(19): 1798-1800.
[138]Chen Y, Chen L, Deng Q, Zhang G, Wu K, Ni L, et al. The presence of SARS-CoV-2 RNA in the feces of COVID-19 patients. *Journal of Medical Virology*. 2020; 92(7): 833-840.
[139]Perisetti A, Goyal H, Gajendran M, Boregowda U, Mann R, Sharma N. Prevalence, mechanisms, and implications of gastrointestinal symptoms in COVID-19. *Frontiers in Medicine (Lausanne)*. 2020; 7: 588711.
[140]Lin L, Jiang X, Zhang Z, Huang S, Zhang Z, Fang Z, et al. Gastrointestinal symptoms of 95 cases with SARS-CoV-2 infection. *Gut*. 2020; 69(6): 997-1001.
[141]Henry BM, de Oliveira MHS, Benoit J, Lippi G. Gastrointestinal symptoms associated with severity of coronavirus disease 2019 (COVID-19): A pooled analysis. *Internal and Emergency Medicine*. 2020; 15(5): 857-859.
[142]Xing YH, Ni W, Wu Q, Li WJ, Li GJ, Wang WD, et al. Prolonged viral shedding in feces of pediatric patients with coronavirus disease 2019. *Journal of Microbiology, Immunology and Infection*. 2020; 53(3): 473-480.
[143]Camargo SM, Singer D, Makrides V, Huggel K, Pos KM, Wagner CA, et al. Tissue-specific amino acid transporter partners ACE2 and collectrin differentially interact with hartnup mutations. *Gastroenterology*. 2009; 136(3): 872-882.
[144]Haroun RA, Osman WH, Eessa AM. Evaluation of serum total sialic acid in moderate COVID-19 patients with and without gastrointestinal tract manifestations. *Tissue and Cell*. 2021; 74: 101679.
[145]Hajifathalian K, Krisko T, Mehta A, Kumar S, Schwartz R, Fortune B, et al. WCM-GI research group*. Gastrointestinal and hepatic manifestations of 2019 novel coronavirus disease in a large cohort of infected patients from New York: Clinical implications. *Gastroenterology*. 2020; 159(3): 1137-1140.
[146]Cheung KS, Hung IFN, Chan PPY, Lung KC, Tso E, Liu R, et al. Gastrointestinal manifestations of SARS-CoV-2 infection and virus load in fecal samples from a hong kong cohort: Systematic review and meta-analysis. *Gastroenterology*. 2020; 159(1): 81-95.
[147]Nobel YR, Phipps M, Zucker J, Lebwohl B, Wang TC, Sobieszczyk ME, et al. Gastrointestinal symptoms and coronavirus disease 2019: A case-control study from the United States. *Gastroenterology*. 2020; 159(1): 373-375.
[148]Xie C, Jiang L, Huang G, Pu H, Gong B, Lin H, et al. Comparison of different samples for 2019 novel coronavirus detection by nucleic acid amplification tests. *International Journal of Infectious Diseases*. 2020; 93: 264-267.
[149]Kannan R, Przekwas A. A multiscale absorption and transit model for oral delivery of hydroxychloroquine: Pharmacokinetic modeling and intestinal concentration prediction to assess toxicity and drug-induced damage in healthy subjects. *International Journal of Numerical Method Biomedical Engineering*. 2020; 36(12): e3403.
[150]Xiao F, Tang M, Zheng X, Liu Y, Li X, Shan H. Evidence for gastrointestinal infection of SARS-CoV-2. *Gastroenterology*. 2020; 158(6): 1831-1833.
[151]Budden KF, Gellatly SL, Wood DL, Cooper MA, Morrison M, Hugenholtz P, et al. Emerging pathogenic links between microbiota and the gut-lung axis. *Nature Reviews Microbiology*. 2017; 15(1): 55-63.
[152]Alkundi A, Mahmoud I, Musa A, Naveed S, Alshawwaf M. Clinical characteristics and outcomes of COVID-19 hospitalized patients with diabetes in the United Kingdom: A retrospective single centre study. *Diabetes Research and Clinical Practice*. 2020; 165: 108263.
[153]Liu F, Long X, Zhang B, Zhang W, Chen X, Zhang Z. ACE2 expression in pancreas may cause pancreatic damage after SARS-CoV-2 infection. *Clinical Gastroenterology and Hepatology*. 2020; 18(9): 2128-2130.
[154]Tang N, Li D, Wang X, Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. *Journal of Thrombosis and Haemostasis*. 2020; 18(4): 844-847.
[155]Han H, Yang L, Liu R, Liu F, Wu KL, Li J, et al. Prominent changes in blood coagulation of patients with SARS-CoV-2 infection. *Clinical Chemistry and Laboratory Medicine*. 2020; 58(7): 1116-1120.
[156]Lippi G, South AM, Henry BM. Electrolyte imbalances in patients with severe coronavirus disease 2019 (COVID-19). *Annals of Clinical Biochemistry*. 2020; 57(3): 262-265.

[157]Darlenski R, Tsankov N. COVID-19 pandemic and the skin: What should dermatologists know? *Clinics in Dermatology*. 2020; 38(6): 785-787.
[158]Joob B, Wiwanitkit V. COVID-19 can present with a rash and be mistaken for dengue. *Journal of the American Academy of Dermatology*. 2020; 82(5): e177.
[159]Ulhaq ZS, Soraya GV. The prevalence of ophthalmic manifestations in COVID-19 and the diagnostic value of ocular tissue/fluid. *Graefe's Archive for Clinical and Experimental Ophthalmology*. 2020; 258(6): 1351-1352.