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**Review Article**

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# An Overview of a Year with COVID-19: What We Know?

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**ABSTRACT**

Over the last year, SARS-CoV-2 caused the infection of more than 80 million people and about 1.8 million deaths. Since the emergence of the first cases in China, this virus has been the focal point of the scientific community and represented the main subject of a large number of research publications. It has been observed that the symptomatology is broad, varying from asymptomatic/mild manifestations to more severe stages of illness, in some cases leading to multi-organ failure and death. Although WHO announced PHEIC since January 30, and invited the researchers to quickly find solutions for diagnosis, monitoring, and treatment, there are currently no COVID-19 specific therapeutic drugs or vaccines clinically approved. This led to losses on multiple levels, such as: high number of deaths, health/financial crisis, job loss, school closures, etc. For these reasons, there is an urgent need to properly understand all aspects regarding this virus in order to successfully develop strategies to manage and stop this pandemic. Hence, this paper analysis the current knowledge and provides a comprehensive overview on this novel coronavirus.

**Keywords:** coronavirus, SARS-CoV-2, viral infection, genomic structure, symptoms

## INTRODUCTION

It's been a year since the new coronavirus emerged in Wuhan, China, and spread rapidly worldwide. So far, World Health Organization (WHO) situation reports mention that there has been reached a total number of more than 80 million SARS-CoV-2 infected persons, of which about 1.8 million people have died (as of December 28).

Coronaviruses (CoVs) are a large family of enveloped viruses, characterized by their surface covered with spikes, resembling with a crown or solar corona. They belong to the Coronavirinae subfamily of the Coronaviridae family, within the Nidovirales order [1]. CoVs are further taxonomically classified into four coronavirus genera: α-CoVs, β-CoVs, γ-CoVs, and δ-CoVs, which are then divided into subgenera or lineages. For example, β-CoV genus is recognized to comprise four phylogenetic lineages (A, B, C and D), of whom the A lineage of β-CoVs has been the focus for CoV packaging studies [1,2]. All these genera can broadly infect various mammals, while only the last two genera (i.e., γ-CoVs and δ-CoVs) can also infect birds [2,3].

Until now, seven CoVs (both low and highly pathogenic viruses), from α-CoVs and β-CoVs genera, have been identified to infect humans, leading to respiratory, hepatic, gastro-intestinal, and neurological diseases [2-5]. Starting with 1960, the first two human coronaviruses (HCoVs) have been discovered in the α-CoVs (HCoV-229E) and β-CoVs (HCoV-OC43) genera, usually causing mild to moderate upper respiratory tract infections [6]. However, for immunocompromised or elderly patients, CoV infections can sometimes escalate into more serious stages of disease.

In November 2002, a novel and more serious strain of β-HCoV (SARS-CoV), originated in bats, generated a severe pneumonia outbreak that spread from South China and reached 37 countries [7]. SARS-CoV led to more than 8000 cases of infected people, and an approximated mortality rate of 10% [8]. The SARS-CoV pandemic was finally extinguished in 2004, by drastic public health measures.

Due to research interest triggered by the impact generated by the SARS-CoV outbreak, in the same year, another HCoV has been identified in the α-CoVs genera (namely HCoV-NL63), and a year later, in 2005, one in β-CoVs genera (namely HCoV-HKU1) [9]. However, both of these new HCoVs were classified of low pathogenicity, as also seen for HCoV-229E and HCoV-OC43, which led to only moderate illnesses like common colds.

Seven years later, in June 2012, another noteworthy pathogenic HCoV (i.e., MERS-CoV) infection caused an outbreak of severe pneumonia, which started in Saudi Arabia [10]. As in the case of SARS-CoV, MERS-CoV originated in bats and was transmitted to humans probably through dromedary camels, as intermediary reservoirs [11]. Although, it was not characterized by such high human-to-human transmission as SARS-CoV, MERS-CoV reached about 27 countries, infecting more than 2494 persons, and registered a fatality rate as high as 36% [11].

In December 2019, the Chinese city of Wuhan has been confronted with several patients presenting pneumonia caused by an unidentified microbial infection. Among the spectrum of various severity flu-like symptoms reported, there have been mentioned fever, cough, dyspnoea and acute

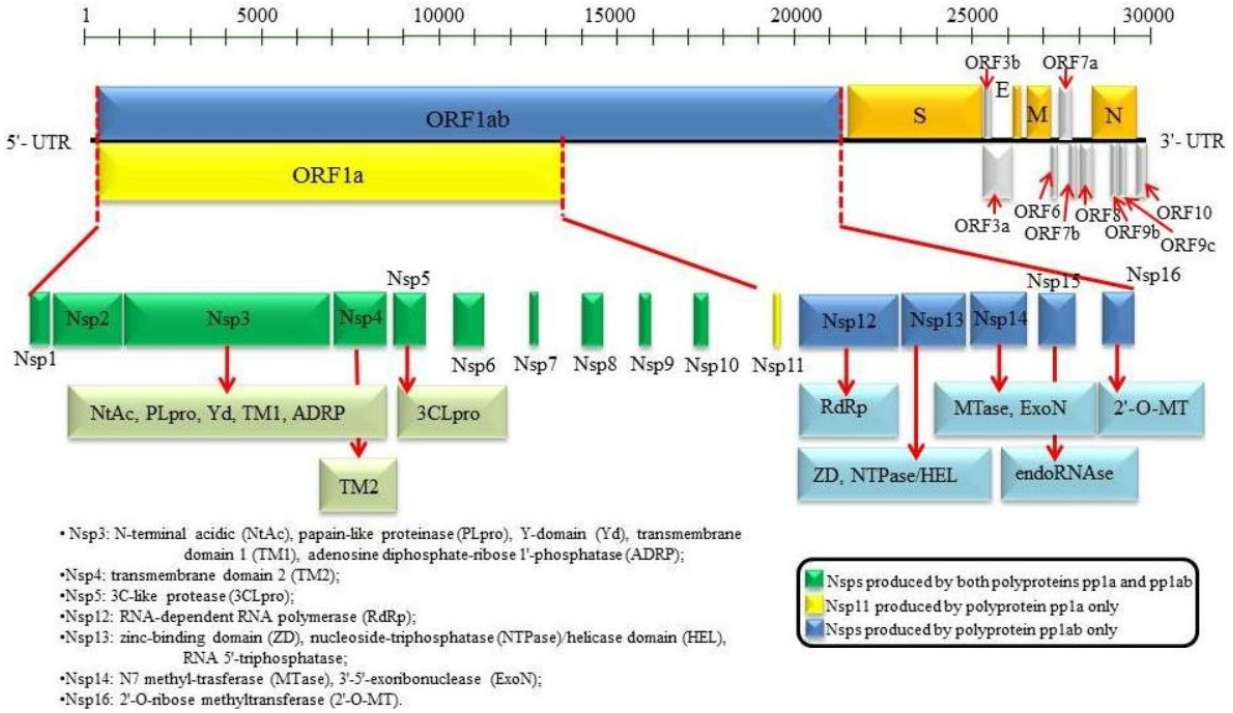


**Figure 1.** The genomic structure of SARS-CoV-2

respiratory distress syndrome (ARDS) [5]. Shanghai Public Health Clinical Centre has revealed the full virus genomic sequence analysis of five patients hospitalized with this new pneumonia, discovering a β-CoV strain unidentified previously, which has an identity of 88% with typical sequence structure of two bat-derived SARS-like CoVs (i.e., bat-SL-CoVZC45 and bat-SL-CoVZXC21) and an identity of 50% with MERS-CoV [12]. International Virus Classification Commission has named this novel β-CoV strain as SARS-CoV-2 [5]. Soon, the epidemiological studies revealed that a majority of infected persons are related to the Huanan Seafood Wholesale Market (patients were deliverymen or sellers in the market), which led to the possible conclusion that the virus suffered animal-to-human transmission [13]. However, human-to-human transmission was also confirmed after 15 health-care practitioners, from Wuhan hospital, were infected due to contact with infected patients [14]. At the end of January 2020, WHO officially named this new pathogen as 2019-nCoV, and the novel infectious disease as COronaVIrus Disease 2019, or COVID-19, was declared as Public Health Emergency of International Concern (PHEIC) [2,15]. COVID-19 has spread worldwide with an alarming escalating rapidity, challenging humans to face a battle with an enemy whose weaknesses are not yet known. Although SARS-CoV-2 has a great genetic similarity with SARS-CoV and MERS-CoV, it has been shown to present a lower pathogenicity, but a higher transmissibility. Thus, the reproduction number ($R_0$), which is a metric for transmissibility, reported for SARS, MERS and seasonal influenza viruses was: 3.1-4.2 [16,17], <1.0 [18,19], and 1.8 [20] respectively; while the $R_0$ for SARS-CoV-2 was seen to range from 2.8 to 5.5 globally [21], while a medium $R_0$ of 4.5±1.44 was reported for European Union [22].

Since this new type of coronavirus emerged, thousands of research papers have been published. All these resources are important building blocks towards finding efficient methods to deal with this pandemic. In this regard, the present paper aims to offer a comprehensive overview on the current knowledge on this topic, thus helping the readers to find summarized in one place the most important aspects regarding virus structure and genomic analysis, infection mechanism and replication, virus strategies to evade host's immune system recognition, infected organs and clinical manifestation. It is hoped that the information analysed here will represent a valuable starting point for future studies.

## STRUCTURE AND GENOME OF SARS-CoV-2

Three weeks after the hospitalization of patient 0 in China, several research groups analysed the viral strain isolated from patients airway epithelial cells and revealed the sequencing of SARS-CoV-2 genome [23,24]. The phylogenetic tree has been presented in several papers [25,26]. From these studies, the genomic similarities with other known CoVs, in general, and with SARS-CoV, in particular, are very evident. Thus, it has been shown that the closest relatives of the newly identified 2019-nCoV are several bat-derived CoVs, like bat-CoV-RaTG13 (with ~96.3% sequence similarity), followed by two bat SARS-like CoVs (with ~88% sequence similarity): bat-SL-CoVZC45 (NCBI accession no MG772933) and bat-SL-CoVZC21 (NCBI accession no MG772934) [12,23,27]; while sequence similarity with SARS-CoV is ~79% and MERS-CoV is ~50% [12,15,28,29]. The genomic structure is characteristic to the lineage B, from β-COVs genus, and comprise a positive-sense single-stranded ribonucleic acid (+ssRNA) genome, surrounded by a membrane envelope [12,28]. As seen for other identified CoVs RNA genomes, which have sizes varying from 26 000 to 37 000 bases [7,30], the SARS-CoV-2 genome length was also identified to fall within these parameters, containing 29 891 nucleotides (GenBank no. MN908947) [28]. These are arranged into 14 open reading frames (ORFs), which encode 27 proteins responsible for viral RNA synthesis [7]. Thus, the SARS-CoV-2 genome structure is comprised of a 5'-cap and a 3'-poly(A) tail, as follows: 5' - Leader untranslated region (UTR) - Replicase - Spike (S) - Envelope (E) - Membrane (M) - Nucleocapsid (N) - 3' Trailer UTR (**Figure 1**) [7,31]. The first two functional ORFs (ORF1a and

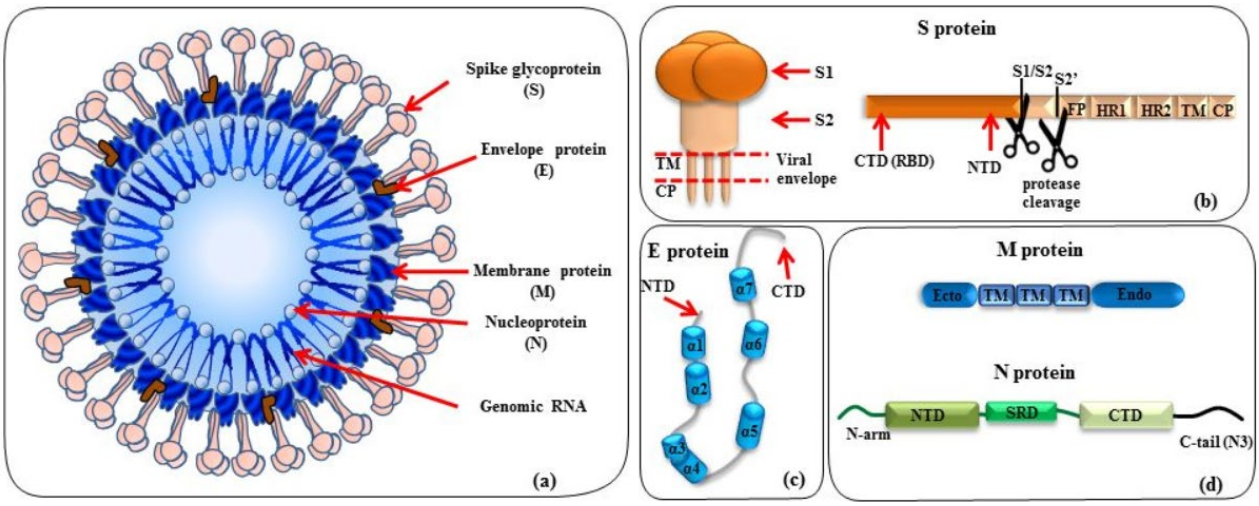


**Figure 2.** SARS-CoV-2 structure (a) and component proteins: S protein (b), E protein (c), M and N proteins (d)

ORF1ab) are situated at the 5'-cap of the genome and constitute approximately 67% of viral RNA. These ORFs encode two large polyproteins (pp1a, pp1ab), which are proteolytically cleaved into 16 non-structural proteins (Nsps), which are Nsp1-16, and have been reported to constitute the replicase-transcriptase complex (RTC) [28]. The RTC includes several enzymes, such as papain-like protease (PLpro)/adenosine diphosphate-ribose 1'-phosphatase (ADRP) - Nsp3, chymotrypsin-like protease (3CLpro) - Nsp5, primase complex - Nsp7/8, RNA-dependent RNA polymerase (RdRp) - Nsp12, nucleoside-triphosphatase (NTPase)/helicase (HEL)/RNA 5'-triphosphatase - Nsp13, N7 methyl-transferase (MTase)/3'-5'-exoribonuclease (ExoN) - Nsp14, endoRNAse - Nsp15, and 2'-O-ribose methyltransferase (2'-O-MT) - Nsp16 [32-34]. These Nsps possess various functions: Nsp1 inhibits host antiviral response, Nsp3/4/6 complex is responsible for viral replication, Nsp7/8 complex is part of RNA polymerase, Nsp9 contributes to ssRNA binding, Nsp10 is necessary for methyltransferase activity of Nsp16, Nsp12 catalyses the replication of viral RNA, ExoN of Nsp14 is responsible for proofreading of viral genome, Nsp15 contributes both to replication, as well as blocking the host's immune system [32,33].

The other 33% at the 3'-terminus of SARS-CoV-2 viral genome consists of 13 ORFs, which are expressed from 9 predicted subgenomic RNAs (sgRNAs). Among these, four important structural proteins, in an invariable sequence order, are: Spike (S) - Envelope (E) - Membrane (M) - Nucleocapsid (N) (which contribute to viral structure and infection), and nine interspersed accessory proteins (ORF3a, ORF3b, ORF6, ORF7a, ORF7b, ORF8, ORF9b, ORF9c and ORF10), some of which present essential functions in viral pathogenesis [5,34].

The spike glycoproteins (Mw ~ 150 kDa) are multifunctional molecular machines, displayed on the virus surface in a corolla assembly, and are known to play an essential role in virus attachment to host cell receptors, mediating entry and tissue tropism (**Figure 2a**). They are composed of three intertwined polypeptide protomers (a large ectodomain, a single-pass transmembrane (TM) protein anchor and a short intracellular tail) which, depending on the CoV species, possess different 3D conformations and lengths varying between 1100-1600 amino acid residues (**Figure 2b**) [1,7,35]. The ectodomain of S protein comprises two functional subunits (S1 and S2), with roles in receptor recognition, proteolytic cleavage and fusion with host cell membrane [36]. S1 subunit includes two independently folded domains, N- and C-terminal domains (NTD and CTD), of which CTD serves as the receptor-binding domain (RBD) [37]. RBD facilitates recognition and direct attachment of S domain B ($S^B$) to the angiotensin-converting enzyme 2 (ACE2) cell receptors [7,38]. Also, S1 subunits stabilize the S2 pre-fusion state [38]. S2 subunit contains the fusion peptide (FP), two heptad-repeat 1 and 2 domains (HR1 and HR2), TM and cytoplasmic (CP) regions [1,28,39]. S protein requires a two-step sequential mechanism for activating its fusion potential [40]. Thus, a protease cleavage occurs first at the S1 and S2 subunits boundary, and a second cleavage at S2' site, located in the FP vicinity [37]. This cleavage triggers extensive irreversible conformational changes (pre- and post-fusion), and has been reported to be facilitated by one or several host cellular proteases, like human airway trypsin (HAT)-like protease, transmembrane protease serine 2 (TMPRSS2), TMPRSS4, furin, and cathepsins [41-47]. As a result, the synergistic activity of RBD and the presence of host proteases determine the complex process of CoV entry into target cells. While S2 subunit has been seen to be highly conserved, presenting a 99% similarity with that of SARS-CoV S2 [12,28], overall identity between S protein of SARS-CoV-2 and SARS-CoV is about 87% [34].

The E protein (**Figure 2c**) is a short, integral membrane pentameric protein, with a 3D structure composed of five subunits, each having a large hydrophobic TM domain of seven α-helices and eight loops, flanked by a short hydrophilic amino-terminal (NTD) and a long carboxyl (CTD) one [48]. The hydrophobic TM domains oligomerise and modulate the formation of ion conductive channels, which are important for pathogenesis. It has been reported that E protein of SARS-CoV-2 is highly conserved, being identical to that of other bat CoVs (ZXC21, ZC45, RaTG13) and pangolin CoV (MP798) [49]. Also, the E protein plays an important role in virus life cycle, such as in viral genome assembly, envelope formation and virus release [50,51]. Finding ways to inhibit the ion channels might lead to developing anti-SARS-CoV-2 drugs [48].

The M glycoprotein is also highly conserved and more widely spread within the virus membrane than E protein. It consists of three TM domains flanked by a short $NH_2$-terminal domain (ectodomain), exposed outside the virion surface, and a long COOH-terminal cytoplasmic domain inside (endodomain) (**Figure 2d**) [11,52,53]. The endodomain globular structure is compact, thus only a short carboxy-terminal tail allows binding with other proteins [11]. The M proteins have an important role in virus assembly and, along

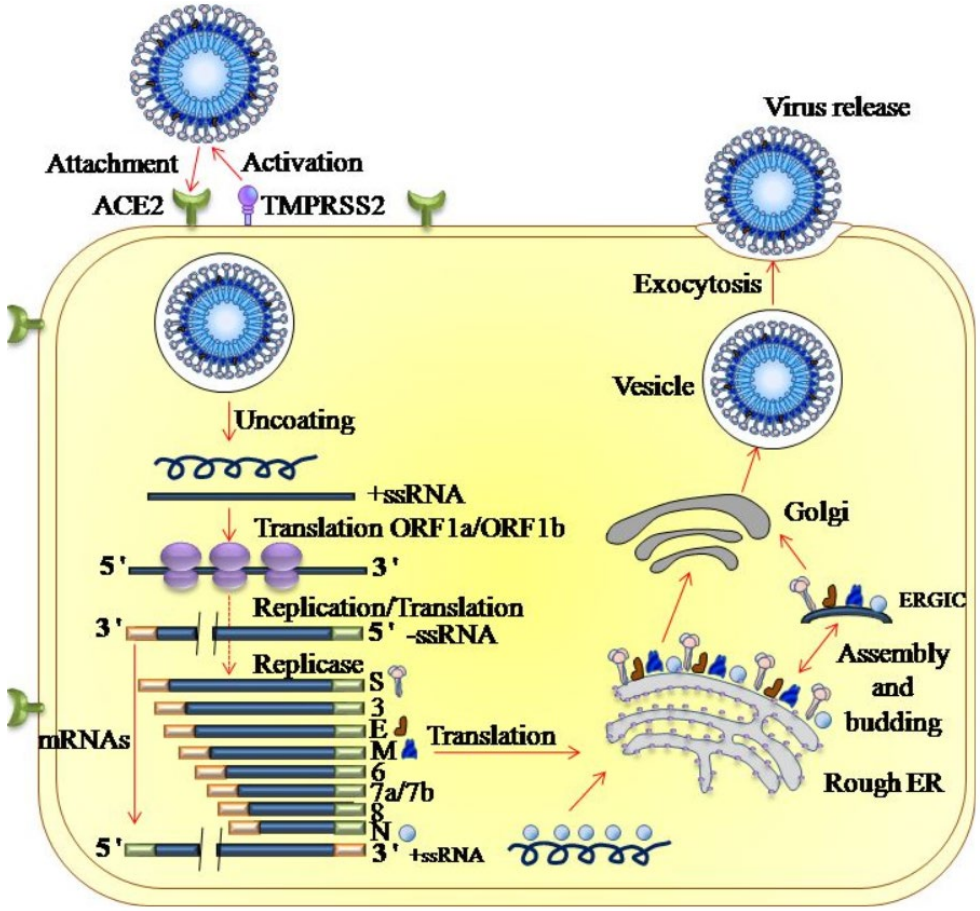


**Figure 3.** SARS-CoV-2 entry into the host's cell and virus life cycle. Viral S protein, activated by TMPRSS2, attaches to cellular ACE2 receptor and facilitates entry into host cell. Genomic RNA is released and the replication/translation starts. The assembly of viral particles and gRNA into virions takes place in ERGIC. Newly formed virions are released through exocytosis

with S and E proteins, are encapsulated in a membrane envelope [11].

Inside the membrane envelope, the nucleocapsid phosphoprotein is formed through binding between N protein and genomic RNA (gRNA). N protein contains two independent structural modules (NTD and CTD), followed by an acidic carboxy-terminal domain (N3) (**Figure 2d**). Between NTD and CTD is present a central linker serine- and arginine-rich domain (SRD). NTD is responsible for RNA-binding, CTD is capable of self-association, while the central linker SRD interacts with the M protein [54]. N plays essential roles in packaging the +ssRNA into a helical ribonucleoprotein (RNP) complex [55], proper development of the protective capsid and full virus structure [1,7,35]. During viral infection, N protein is the most abundantly distributed in host cells cytoplasm and, in order to facilitate efficient virus transcription and replication, it must easily disintegrate to release the gRNA [55].

Although the newly identified virus has been shown to present remarkable homology with previous SARS-CoV, is suspected that it suffered some function mutations, making it more transmissible and infectious. The similarity between the two SARS viruses is in regard to their ORF1ab (which encode 16 Nsps), as well as the four common structural proteins (S, E, M, N). However, S protein of SARS-CoV-2 has only 87% similarity with that of SARS-CoV, while the other three structural proteins (E, M, and N) have more than 94% identity to their SARS-CoV homoloques [34]. Also, other differences are related to the accessory proteins. Thus, SARS-CoV-2 has 85.1% similarity in ORF3a with SARS-CoV, while ORF3b is only 9.5% similar, having only 22 amino acids in SARS-CoV-2, in contrast with a longer 3b protein of 154 amino acids of SARS-CoV [34,56]. Also, the ORF8 of SARS-CoV-2 is intact, with only 45.3% similarity with ORF8a and 8b of SARS-CoV. In addition, SARS-CoV-2 possesses ORF10, which is not detectable in SARS-CoV [34].

## SARS-CoV-2 ENTRY INTO HOST CELLS AND REPLICATION

The proposed mechanism of infection used by SARS-CoV-2 has been seen to be similar with other β-CoVs, among which SARS-CoV also. However, subtle genetic changes exhibited by this new CoV may have significantly affected its pathogenicity. CoVs make use of their homotrimeric spikes S glycoproteins (i.e., S1 and S2 subunits in each spike monomer) to attach to a specific receptor of the host's cells and facilitate subsequent virus entry (**Figure 3**). This cellular receptor is known to be ACE2 [15]. Upon binding to ACE2, S protein is proteolytically cleaved by host proteases at the boundary between S1 and S2 subunits [1]. This cleavage leads to a conformational shift that triggers S2 activation and a second cleavage at S2' site, located upstream FP. Further, FP penetrates the cell membrane, facilitating fusion. Cryo-EM studies revealed that RBD within the S1 subunit is the key functional component through which the binding between SARS-CoV-2 and ACE2 is made [57]. So, RBD plays a critical role in the viral life cycle, enabling the cell fusion and transport of the viral genetic material inside the host cell. Although it has been reported that SARS-CoVs have

similar infection mechanisms, SARS-CoV-2 RBD exhibits higher binding affinity than SARS-CoV, which may explain the higher rate of human-to-human transmission [58,59]. A good knowledge of host's ACE2 receptors and their targets might significantly contribute to drug development. Also, inhibiting virus binding and entering the cell might represent another path to efficient drug discovery. Cellular proteases like HAT-like protease, TMPRSS2, furin, and cathepsins are involved in CoVs mechanism of entering host cell, by splitting the S protein to further penetrate the cell membrane [43,60]. Thus, the development of inhibitors of these proteases might represent efficient targets for SARS-CoV-2, as has been seen in HIV/AIDS treatment. For example, a recent study published by Hoffmann and co-workers describes the serine protease TMPRSS2 contribution to S protein priming for entering the cell and proposes, as a treatment option, a clinically approved TMPRSS2 inhibitor to block S protein entry [61]. However, further investigations on S proteins and the RBD-ACE2 interaction may reveal essential insights for drug development and vaccine design to fight against COVID-19.

After virus entry into the cell, there are several aspects that need to be considered. First, the enzymes present on the surface of the host cells cleave the ACE2 receptors, shedding them into the extracellular environment, which has been reported to increase permeability of pulmonary capillaries and damage alveoli [62]. Second, the virus needs to replicate its RNA in order to survive. However, as has been seen for SARS-CoV, the SARS-CoV-2 replication mechanism is very complex and until now insufficiently understood, thus hampering the development of efficient strategies to fight against this type of infection [63]. In order to replicate, SARS-CoV-2 is transported to endosomes and then it releases its gRNA into the cytoplasm. Here, it uses the host cells ribosomes to create its own viral proteins [5]. In addition to the replication of the progeny gRNA, there are also numerous intermediate negative-strand products that serve as mRNAs for various sgRNAs [11]. These sgRNAs are translated into the viral structural (S, E, and M) and accessory proteins, which are further insulated in the endoplasmic reticulum, and then transported to the endoplasmic reticulum-Golgi intermediate compartments (ERGIC) [64]. Nucleocapsid is formed by assembling of replicated gRNA and N protein and also transported to ERGIC. Here, the new viral particles are assembled into small vesicles. Then, the viral particles fuse with the cell membrane and are released through exocytosis. In this process, the infected cells are damaged, and the virus travels to infect other cells. Since Nsps have an important role for SARS-CoV-2 replication mechanism, it is anticipated to be potential targets for emerging strategies against this viral infection [11].

## IMMUNE SYSTEM RESPONSE TO SARS-CoV-2 INFECTION

In general, human body's first reaction to the presence of viruses is mediated by innate immune system, that can detect the differences between cellular molecules and pathogens, and alerts host cells. Specific Pathogen-Associated Molecular Patterns (PAMPs) of viral components and intermediate replication products (such as: glycoproteins, lipoproteins and other molecules which are produced during the life cycle of the virus, but which are not normally present among usual cellular components) and Damage-Associated Molecular Patterns (DAMPs), triggered by cell damage/death, are detected by Pattern Recognition Receptors (PRRs) present in/on host antigen presenting cells (APCs), like dendritic cells, monocytes, macrophages, and neutrophils [65]. These PRRs can be membrane-bound (such as Toll-like receptors (TLRs)) and cytoplasmic (such as Nucleotide-binding oligomerization domain (NOD)-like receptors (NLRs) and Retinoic acid-inducible gene I (RIG-I)-like receptors (RLRs)), leading to different biological signalling that further activates an antiviral response [30,66].

TLRs are a class of ten sensors bound on cell membranes, like cell surface receptors (TLR1, TLR2, TLR4, TLR6, TLR10) and endosomal receptors (TLR3, TLR7, TLR8, and TLR9), which can detect viral PAMPs and, by recruiting adapter proteins (like myeloid differentiation primary response 88 (MyD88) protein, toll-interleukin 1 receptor (TIR) domain containing adaptor protein (TIRAP), TIR-domain containing adapter inducing interferon-β (TRIF), and TRIF-related adaptor molecule (TRAM)) in immune cells, propagate the antigen-induced signal transduction pathway. The signalling pathways can be MyD88-dependent (leading to NF-kB activation and subsequent pro-inflammatory cytokines release) or TRIF-dependent (triggered by dsRNA and leading to activation of interferon regulatory factor 3 (IRF3), production of Type 1 Interferon (T1-IFN), and activation of late-phase NF-kB). For example, TLR4 can detect S protein of CoVs and, through the MyD-dependent signalling pathway, triggers the release of pro-inflammatory cytokines [67], while TLR3 can recognize dsRNA of CoVs and, through TRIF adapter protein, further leads to increased release of pro-inflammatory cytokines (like IFN-β) via phosphorylation and nuclear translocation of IRF3 and activation of NF-kB transcription factors [64,68].

RLRs are sensors present in cell's cytoplasm (like RIG-I and melanoma differentiation-associated 5 (MDA5) receptors) that recognize PAMPs of viral RNA, and trigger antiviral signalling through their activated caspase-recruitment domains (CARDs) and CARDs of mitochondrial antiviral signalling proteins (MAVSs). This binding further leads to the recruitment of TNF receptor-associated factor 3 (TRAF3) and the enzymes complex between inhibitor of NF-kB kinase subunit epsilon (IKKε) and TANK-binding kinase 1 (TBK1), which induces the activation of several transcription factors, like interferon regulatory factor 3 (IRF3) and IRF7. IRF3 and IRF7 promote transcription of T1-IFN (like IFN-α and IFN-β) and T3-IFN (IFN-λ), which further activates Janus kinases-signal transducers and activators of transcription (JAK-STAT) signalling pathway. Activation of JAK-STAT signalling pathway determines the transcription of multitude IFN-stimulated genes (ISGs), that further intensify the IFN production [68,69].

NLRs are able to detect the production of reactive oxygen species (ROS) [70,71]. The ligand recognition determines the NLR binding with the adaptor protein Apoptosis-associated speck-like protein containing a CARD (ASC, or PYCARD) and, in addition to activated caspase-1, is employed in the inflammasome formation. Caspase-1 proteolytically processes and activates the pro-inflammatory cytokines Interleukin-1β (IL-1β) and IL-18, which further activates the downstream inflammatory response [68].

The response of body's immune system to SARS-CoV-2 infection has been reported to be generally similar to SARS-CoV and MERS-CoV [66,72], which managed to suppress the defence mechanisms of immune system, mentioned above, and cause more severe stages of disease [73-75]. For example,

SARS-CoV alters the activity of RIG-I and MDA5 sensors and inhibits MAVS activation, leading to impaired activation of IRF3 nuclear translocation [69]. Moreover, it also inhibits TRAF3 and TRAF6, which play an important role in IRF3/7 activation triggered by TLR 3/7 and/or RIG-I binding to MDA5 [74]. Although the IFN antagonizing activity of several individual SARS-CoV proteins has been characterized in cell cultures, in vivo response of innate immune system to SARS-CoV infection might be significantly different. During viral infection, these proteins form large complexes and their synergistic activity in modulating innate immune signalling has not been yet understood [76].

To evade antiviral response of immune system, SARS-CoV-2 developed several avoidance strategies to block the cellular PRRs recognition, both before and after host cell entry stages. One of these strategies is represented by Double Membrane Vesicles (DMVs) developed by the virus, which might shield the PAMPs of viral intermediate dsRNA from being detected by cytosolic PRRs [5]. Moreover, the virus makes use of its encoded non-structural, structural and accessory proteins as antagonists of innate immune molecules. For example, Nsp1 can inhibit the T1-IFN function by suppressing the activity of translational machinery of the host cell, degrading the host mRNA, or by inhibiting the phosphorylation of STAT1 transcription factor [77]. T1-IFN inhibition in the early stage of the infection allows the viruses to freely replicate and spread in the body, thus leading to a more severe stage of the disease [30,72]. Nsp3 is also able to protect SARS-CoV-2 from immune system activity, through its encoded proteins, like PLpro and macrodomains. PLpro can block the IRF3 phosphorylation [78] and also can disrupt NF-kB signalling [79], thus antagonizing IFN. Another study reported that mice infected with SARS-CoV-lacking macrodomains presented no lung pathology and an increased survival rate, although the expression of T1-IFN, ISG15, CXCL10 and the pro-inflammatory cytokines IL-6 and TNF was high [80]. Thus, by inhibiting the function of these two proteins of Nsp3 may help the immune cells to hinder the virus replication. Nsp7 and Nsp15 can also function as IFN antagonists [79]. Another aspect that could have been a weak point in viral mRNA structure, thus facilitating its differentiation from host cell RNA and recognition by the immune cells, is represented by the missing 5' cap. However, the virus developed a mechanism to imitate the capping machinery of host cells, through its Nsp14 and Nsp16 [81,82]. Thus, an RNA cap (similar to host's RNA cap) is built by the guanine-N7-methyltransferase activity of Nsp14 [81,83] and modified by the 2'-O-methyl-transferase activity of Nsp16 [84,85], making it unrecognizable by host PRRs [76]. In addition to IFN antagonist function of Nsps, the structural proteins of SARS-CoV-2 virion might also block the innate immune responses. Among them, N protein might inhibit T1-IFN expression [78], while M protein can block IFN-β transcription [86], although these mechanisms are not yet properly understood. There are also reports mentioning that accessory proteins might have functions in evading immune responses. Among them, ORF3b antagonizes T1-IFN signalling pathway, but does not block the activation of NF-kB transcription triggered by TNF-α [87]. In addition, ORF6 accessory protein has the ability to bind to karyopherin-α2 (thus, blocking JAK-STAT signalling pathway) and to karyopherin-β1 on internal membranes (thus, inhibiting nuclear translocation of the transcription factor STAT1) [76,79,88]. However, there are still many unelucidated aspects regarding the ability of SARS-CoV-2 to evade or inhibit the host's innate immune response and drive pathogenesis [89].

In addition to the mechanisms developed by the virus to escape the immune system response, elderly persons or immunocompromised patients might also present a delayed or dysregulated expression of IFNs and ISGs [90]. Thus, viral replication and dissemination in primary infected tissues proceed unhindered in the early stage of the disease. Moreover, virus fragments and intracellular components are released due to infected cell death into extracellular environment, which further leads to the attraction and accumulation at the site of inflammation of large quantities of inflammatory cells (monocytes, macrophages, neutrophils) [5,91]. In contrast, lymphocytes register alarming low levels (lymphopenia) [92]. Among lymphocytes, T cells (especially cytotoxic T cells CD8+ and helper T cells CD4+) play important antiviral role in the adaptive immune response [35]. However, there has been reported that approximately 80% of COVID-19 patients present lymphopenia [13,93,94], including reduced number of cytotoxic T cells CD8+ and helper T cells CD4+ [95], as well as high exhaustion levels and low functional diversity of T cells [95,96]. In contrast, SARS-CoV recovered individuals presented CD4+ and CD8+ memory T cells even after four to six years post infection [97,98], information that might help in developing vaccines [5]. Also, B cells are involved in the production of antibodies, such as Immunoglobulin (Ig) M and IgG [5], but in severe cases of COVID-19 the level of B cells was also decreased [99]. In general, IgM produced during SARS-CoV-2 infection can last about 3 months, while IgG is present in the body for longer periods [64].

Neutrophils can be activated by the inflammatory cytokines, especially IL-8, to secrete particular types of molecules, like ROS, as well as proteases. These molecules try to eliminate the virus, but unfortunately they also damage the surrounding cell tissue. The inflammation can further spread into the systemic circulation, leading to systemic inflammatory response syndrome (SIRS). Afterward, the body tries to fight back by a massive uncontrolled release of pro-inflammatory cytokines (such as IL-1β, IL-2, IL-6, IL-8, IL-12, TNF-α, etc.) and chemokines (C-C motif chemokine ligand (CCL)-2, CCL-3, CCL-5, CXCL8, CXCL9, CXCL10) [100,101] which, in addition to a dysfunctional T cell response, results in hyperinflammation or cytokine storm [13].

## CLINICAL MANIFESTATION

SARS-CoV-2 uses its S protein to attach to ACE2 receptors of host cells, to enter the human body. Thus, this virus can potentially infect all ACE2-expressing cells, such as those in the respiratory system, heart, gastrointestinal tract, kidneys, etc., targeting almost all organs in the body (**Figure 4**). However, approximately 80% of all ACE2-expressing cells are type II alveolar cells in the lungs [102], which have been reported to be highly affected by this virus. In addition to these cells, ciliated and goblet/secretory cells in the upper respiratory tract and nasal mucosa are also affected [102,103]. Although the majority of studies show that SARS-CoV-2 affects respiratory epithelium and pulmonary alveoli [104,105], there are also reports of cardiovascular complications in some COVID-19 patients [106], suggesting that myocardiocytes and vascular endothelia can also be infected [107,108]. In addition, other studies show that the virus also affects the digestive system,

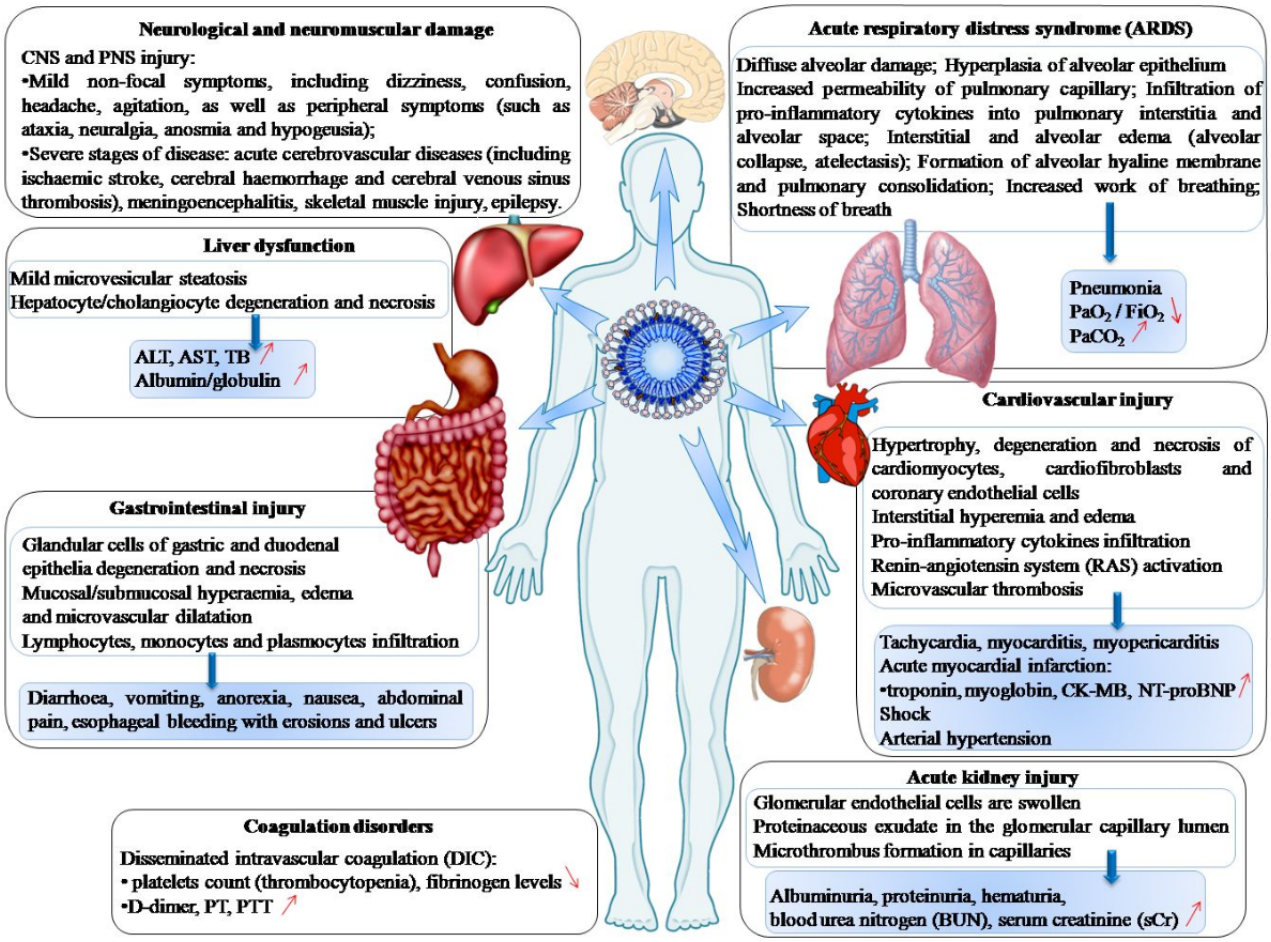


**Figure 4.** SARS-CoV-2 infection symptomatology

since ACE2 is expressed as well in absorptive enterocytes present in the colon and ileum, as well as cholangiocytes [64,109,110]. Moreover, the proximal tubules damage leads to kidney failure. Immune cells (like macrophages, monocytes and T cells) have been observed to be infected by SARS-CoV, although they have a lower ACE2 expression level [69,111,112]. However, it is not yet clearly known if/how SARS-CoV-2 infects these types of immune cells.

## Respiratory System

SARS-CoV-2 infects the respiratory system by attaching to type II pneumocytes in the alveoli. There are actually two different types of pneumocytes in the alveolar walls: type I pneumocytes (which are responsible for gas exchange between alveoli and blood) and type II pneumocytes (which secrete pulmonary surfactant, with role in decreasing the surface tension within alveoli and reducing the collapsing pressure). Viral widespread inflammation of pneumocytes can lead to diffuse alveolar damage and ARDS, which activates the release of immune cells into the alveoli. However, their nonspecific defensive mechanisms contribute to amplification of this situation and lead to further damage of alveolar cells. Moreover, the pro-inflammatory cytokines (like IL-1, IL-6, TNF-α, etc.), released into the pulmonary capillary, lead to increased vascular permeability. As a result, the fluid might start leaking and accumulating into the interstitial spaces (causing interstitial edema, and alveoli compression), and can enter into the alveoli (affecting the surfactant production/concentration and causing alveolar edema). Further, the surface tension is affected, leading to alveolar collapse and atelectasis. In this stage, reopening the alveoli during inhalation is extremely difficult, thus the work of breathing increases. Moreover, high amount of fluid accumulated around the alveoli impairs the proper gas exchange through the alveolar membrane, causing hypoxemia (low arterial partial pressure of oxygen, $PaO_2$) and hypercapnia (increased level of $CO_2$ in the blood, $PaCO_2$). Further, due to insufficient oxygen delivered to the tissues, hypoxemia can lead to shortness of breath (low fraction of inspired oxygen, $FiO_2$). On the other hand, hypercapnia can progress to respiratory acidosis. Also, all the cytokines released affect the vascular endothelium, increasing the expression of a particular type of proteins, called vascular cell adhesion molecules (VCAMs). Leukocytes attach to vascular endothelium, by VCAMs mediation, in order to enter the inflammation area. Thus, if the expression of VCAMs is increased, then more neutrophils and macrophages can reach the affected area, which perpetuate the inflammatory response. In addition, the leukotrienes stimulate the bronchial smooth muscle, causing bronchoconstriction, which further decreases the gas exchange (hypoxemia), exacerbating the already present shortness of breath (or dyspnoea). The accumulation of all damaged cells, protein deposition, macrophages, and neutrophils, form a hyaline membrane and pulmonary consolidation. Also, the cytokines can increase the activity of pro-coagulants, leading to pulmonary embolism.

The inflammation within the lungs can spread into the systemic circulation, leading to SIRS and massive cytokine storm [5,13]. The increased vascular permeability throughout the entire circulatory system causes plasma to start leaking out

and accumulate within the tissue spaces, decreasing overall blood volume (hypovolemia). In addition, vasodilatation leads to decreased total peripheral resistance. In effect, the patient becomes hypotensive, with a decreased perfusion to different organs, heading toward multi-system organ failure [5].

### Cardiovascular Injury

Cardiovascular injury might be triggered by direct viral infection or indirect effect of hypoxemia and cytokine storm [113-115], and has been reported to be one of the major complications and causes of death in SARS-CoV-2 infection (about 77% of COVID-19 patients in intensive care units) [13,94,116]. Moreover, individuals with previous cardiovascular disorders (hypertension, coronary artery disease) are more prone to progress to a severe stage of SARS-CoV-2 infectious disease, with worse cardiac injury [94,117].

As has been reported in SARS-CoV [118] and MERS-CoV cases, SARS-CoV-2 is also a cardiotropic virus, which can directly bind on ACE2 receptors highly expressed in cardiomyocytes, cardiofibroblasts, and coronary endothelial cells [119]. Moreover, SARS-CoV-2 has been reported to contribute to downregulation of ACE2 expression, leading to decreased conversion levels of hydrolysed angiotensin II into angiotensin 1-7 [120]. Angiotensin 1-7 agent plays important protective roles in cardiovascular organs [121] and decreases the production of pro-inflammatory cytokines [120]. Thus, its suppression might trigger elevated risks of vasoconstriction, endothelial dysfunction, oxidative stress, and amplified cytokine storm [122]. Among the reported cardiac dysfunctions are: tachycardia, myocarditis, or myopericarditis [117,122]. Heart injury is expressed by elevated levels of cardiac markers, like creatine kinase myocardial band (CK-MB) (acute myocardial infarction), elevated troponin, which might also lead to increased levels of N-terminal prohormone of brain natriuretic peptide (NT-proBNP), and high myoglobin [94,116,122,123].

### Hepatic and Gastrointestinal Tract Inflammation

Liver dysfunction is another clinical feature reported in SARS-CoV-2 infected patients [124,125], as also seen in previous SARS-CoV [126] and MERS-CoV [127] outbreaks. The incidence of hepatic dysfunctions was registered in 15% to 78% of COVID-19 cases [128]. Among the indicators signalling hepatic injuries, the most encountered are abnormal elevated levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), albumin (ALB)/globulin (GLB) and slightly elevated levels of total bilirubin (TB) [124,129].

The possible mechanism of liver damage in COVID-19 patients, although not yet clearly elucidated, seems to be triggered by both direct viral infection cytopathogenic effect, as well as indirect effect of inflammatory cytokine storm. Although, ACE2 receptors are only slightly expressed in hepatocytes (about 2.6%), they are highly expressed in cholangiocytes (about 59.7%), suggesting that the virus might directly affect biliary duct, further leading to damaged liver activity [130]. Moreover, typical lymphopenia and increased level of C-reactive protein were reported to cause hepatic dysfunctions in severe cases of COVID-19 [125,131]. In addition, individuals with pre-existent liver diseases are more susceptible to contract and develop severe stages of SARS-CoV-2 infections [131,132].

CoVs are also well known to cause gastrointestinal infections [133], with typical symptoms like diarrhoea, vomiting, nausea, and abdominal pain [129,134]. SARS-CoV-2 might attach to ACE2 receptors of glandular cells present in gastric and duodenal epithelia [110] or enterocytes [135], causing absorption dysfunction, abnormal gastrointestinal enzymes secretion and activation of enteric nervous system, leading to diarrhoea [110]. Also, the inflammatory response of immune system might indirectly affect the gastrointestinal tract [134]. There are reports mentioning that COVID-19 patients who did not develop digestive symptoms present higher healing rates (about 60%), as opposed to patients with digestive symptoms (about 34%) [134].

### Kidney Injury

Acute kidney injury has been reported to be a major cause of death in SARS-CoV and MERS-CoV infected individuals (mortality rate around 60% - 90%) [136]. Although early studies reported that acute kidney injury incidence is low (3% - 9%) in SARS-CoV-2 cases [93,94,129], however there are recent reports suggesting higher percentage of renal dysfunction [137,138]. The ACE2 receptors are also expressed in renal tubular cells, thus facilitating viral binding and pathogenesis [136]. Moreover, massive inflammatory syndrome might also lead to kidney damage. Among the clinical features of COVID-19 patients are extremely high albuminuria, proteinuria, haematuria, elevated levels of blood urea nitrogen (BUN) and serum creatinine (sCr) [137,138].

### Coagulation Disorders

Severe cases of SARS-CoV-2 infection have been reported to present a major risk to develop coagulation disorders, like disseminated intravascular coagulation (DIC), which is an imbalance between fibrinolysis and coagulation homeostatic mechanisms [129,139-141]. DIC diagnosis may identify several markers, like abnormally low platelets count (thrombocytopenia) and fibrinogen levels, high fibrin degradation products (like D-dimer), prolonged prothrombin time (PT) and partial thromboplastin time (PTT) [140,142,143]. Clinical features that patients affected by DIC might experience are: shortness of breath, chest pain, increased vascular permeability, leading to widespread haemorrhage and clotting, hypotension, shock, defective organ perfusion, further progressing to multi-system organ failure.

### Neurological and Neuromuscular Damage

CoVs have been reported to cause neurological and neuromuscular symptoms, in addition to their primary pulmonary and gastrointestinal diseases [144-148]. However, the SARS-CoV-2 mechanisms to infect central nervous system (CNS) and peripheral nervous system (PNS) are currently unclear and sparsely treated in literature. The mechanism triggering the neurological damage might be due to either direct viral infection or systemic inflammation. ACE2 receptors are also expressed on the surface of glial cells in the brain and spinal neurons [149], and can potentially facilitate virus neurotropism [150], followed by dissemination through axo-dendritic synapses [33,151]. ACE2 receptors have also been reported to be found both in olfactory epithelium, as well as vascular endothelium [149,152]. Thus, the virus may enter the brain by first infecting nasopharyngeal mucosa, and then spreading through the cribriform bone [153]. A second route might be through haematogenous viremic dissemination of infected endothelial cells and leukocytes, crossing blood brain barrier and leaking into the brain [149,154]. Neurological swelling and brain edema can result from several other

pneumonia-associated factors, like peripheral vasodilatation, hypoxia and hypercarbia, further leading to neurological dysfunction [155].

Reported symptomatology of CNS and PNS damage associated to COVID-19 is diverse, and varies depending on the stage of the disease [156-160]. Thus, some reports mention that early stage of the disease may be accompanied by mild non-focal symptoms, including dizziness, confusion, headache, agitation, as well as peripheral symptoms (such as ataxia, neuralgia, anosmia and hypogeusia) [13,116,161-163]. However, more severe neurologic and neuromuscular damage have also been reported in severe stages of COVID-19, like acute cerebrovascular diseases (including ischaemic stroke, cerebral haemorrhage and cerebral venous sinus thrombosis), meningoencephalitis, skeletal muscle injury, epilepsy [157,161,164].

## MULTI-LEVEL IMPACT OF COVID-19

Over the last year the entire world population was faced with very hard time of the ongoing COVID-19 pandemics. In this context, multi-level challenges are affecting various aspects of our lives. Besides obvious medical impact [165], COVID-19 pandemics led to serious perturbations in social [166-168], economic [166], or education [169,170] sectors, to name just a few.

Due to the novelty and severity of this type of coronavirus, which was predicted to be highly transmissible even since its appearance, National authorities around the world adopted (based on WHO recommendations) various preventive measures (such as hand hygiene, wearing masks, social distancing or quarantine). Almost each country encountered difficulties to implement these measures, thus leading to a rapid spread of the virus. One of the reasons is represented by the lack of population response to these preventive measures, mainly triggered by absence of trust in political/medical authorities and poor health education, encountered even in the developed countries. Moreover, some health instructions (e.g., the „correct" way for mask wearing, hand washing, sneezing, coughing) presented on social media, radio or television programmes demonstrate miss-understanding of virus spread preventing measures. In this context, there is of paramount importance to properly educate the population on a large scale about basic health measures. The population health education should be implemented especially in schools, as well as at the workplace or in healthcare facilities. Investing in population health education might shorten the period of current COVID-19 pandemic, as well as limiting the impact of future health hazards [167].

The education sector is also suffering from the current pandemic. In order to limit virus spread, educational institutions worldwide, from kindergartens to universities, were forced to re-adjust their academic calendar or even close their doors. Courses, exams, and graduations have been postponed or even cancelled. Teachers, students, and parents needed to readapt on a short time notice their entire activity, and quickly learn various online tools with which they were not familiar before. Although some prestigious universities (e.g. Harvard, Yale, Oxford, Cambridge, MIT) have been using the online teaching programmes for several years and are accustomed to E-learning technologies [169], the majority of educational institutions around the world were overwhelmed by implementing the online learning activities, due to lack of appropriate infrastructure (computers, recording platforms) and technical support, absence of previous training for teachers/students to utilise the online platforms and different online learning tools.

Some studies listed the advantages that students mentioned when questioned about online learning system in contrast with traditional methods of learning [169,170]. Thus, some students affirm that they have better academic performances, and they tend to be more organized when studying online, since they have more control over their learning resources and more time to internalize the information.

However, there are also several difficulties encountered during E-learning process: financial issues (high cost necessary for learning resources, like laptop/tablet/phone and internet data), no internet access or slow connectivity, inadequate environment (multiple family members present in the room). Moreover, some professors limited their teaching activity to posting their courses in PowerPoint slides, which is not a proper online teaching method. Due to incapacity to adequately benefit from the online learning systems, many students manifested high level of worry, agitation, and stress concerning homework, quizzes, or the coming exams. However, further studies are required in order to monitor the long-term impact of online education, in contrast with face-to-face delivery of knowledge, and adverse effects both on students and teachers [169,170].

Another significant issue that was observed during the current health crisis is a spectrum of mental health disturbances and sequelae (such as sleep disorders, stress, panic, depression, and anxiety), manifested by recovered COVID-19 patients, as well as other people who did not get infected (medical staff, family members, unemployed or elderly people) [166,168]. Among the aspects that contributed to these mental alterations are loneliness due to social isolation and quarantine, loss of jobs, alarming news presented by mass-media, worry for the consequences of infection, long hospitalization, near-death experiences, death of family member, etc. There is well-known that a deteriorated mental state affects the immune system activity, thus leading to more frequent illnesses and for longer periods of time. In this context, there is an urgent need to develop counselling programmes and psychiatric care to support the mentally affected individuals (telephone assistance, hotlines, or online forums). However, other more profound alterations on psychological level of people suffering due to COVID-19 pandemic might be visible only after months or years later, thus increasing the need for psychiatric assistance [168].

## CONCLUSIONS AND FUTURE PROSPECTS

Over the last year, the entire world was faced with the third coronavirus-induced pandemics of the 21$^{st}$ century, after SARS-CoV and MERS-CoV outbreaks. Since SARS-CoV-2 emergence in Chinese city of Wuhan, the scientific community joined efforts in order to find solutions to eradicate this virus. The genomic analysis of the virus revealed its similarity with several bat-derived CoVs, among which bat-CoV-RaTG13 has a sequence identity of ~96.3%, while previous SARS-CoV has a genetic identity of ~79%. SARS-CoV-2 has been seen to possess different strategies to evade host's immune system

recognition, thus making this virus more transmissible and infectious. Mediated by S protein binding to ACE2 receptors of host cells, SARS-CoV-2 enters the human body and infects the respiratory system, gastrointestinal tract, liver, heart, brain, kidneys, etc. In severe cases, it leads to a massive cytokine storm and multi-organ failure. Given the massive impact of this virus in all aspects of our lives, and since there are currently no specific anti-SARS-CoV-2 drugs or vaccines clinically approved, synergistic efforts into finding solutions to stop this pandemic are of paramount importance. Thus, there is an urgent need for fast and highly precise detection methods, as well as safe and efficient treatment strategies. These can be accomplished only with a good understanding of SARS-CoV-2 structure and mechanisms of infection. In this regard, the present paper aims to offer a comprehensive overview on this novel type of coronavirus.

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