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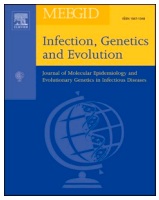

Review

Understanding on the possible routes for SARS CoV-2 invasion via ACE2 in the host linked with multiple organs damage

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ABSTRACT

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), accountable for causing the coronavirus diseases 2019 (COVID-19), is already declared as a pandemic disease globally. Like previously reported SARS-CoV strain, the novel SARS-CoV-2 also initiates the viral pathogenesis via docking viral spike-protein with the membranal angiotensin-converting enzyme 2 (ACE2) — a receptor on variety of cells in the human body. Therefore, COVID-19 is broadly characterized as a disease that targets multiple organs, particularly causing acute complications via organ-specific pathogenesis accompanied by destruction of $ACE2^{+}$ cells, including alveolus, cardiac microvasculature, endothelium, and glomerulus. Under such circumstances, the high expression of ACE2 in predisposing individuals associated with anomalous production of the renin-angiotensin system (RAS) may promote enhanced viral load in COVID-19, which comparatively triggers excessive apoptosis. Furthermore, multi-organ injuries were found linked to altered ACE2 expression and inequality between the ACE2/angiotensin-(1–7)/mitochondrial Ang system (MAS) and renin-angiotensin-system (RAS) in COVID-19 patients. However, the exact pathogenesis of multi-organ damage in COVID-19 is still obscure, but several perspectives have been postulated, involving altered ACE2 expression linked with direct/indirect damages by the virus-induced immune responses, such as cytokinin storm. Thus, insights into the invasion of a virus with respect to ACE2 expression site can be helpful to simulate or understand the possible complications in the targeted organ during viral infection. Hence, this review summarizes the multiple organs invasion by SARS CoV-2 linked with ACE2 expression and their consequences, which can be helpful in the management of the COVID-19 pathogenesis under life-threatening conditions.

1. Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is classified as a positive-sense single-stranded ribonucleic acid (+ssRNA) human coronavirus (HCoV) from the Coronaviridae family, which emerged at the end of 2019 in Wuhan Hubei Province, China, and was later announced as a global pandemic by World Health Organization (WHO) (WHO, 2020). In an attempt to identify this novel viral strain, analysis of whole-genome sequence revealed a 79.5% sequence similarity for SARS-CoV-2 against earlier reported severe acute respiratory syndrome coronavirus (SARS-CoV) strain; hence, positioned under the type of SARS-related HCoVs (Zhou et al., 2020a). Typically, the clinical symptoms of COVID-19 triggered by SARS-CoV-2 included mild to severe respiratory signs, such as acute respiratory distress syndrome (ARDS)/acute lung injury and high mortality prompted by extreme multi-organ failure, particularly in human populations with advanced age, cardiovascular diseases, or diabetes (Chan et al., 2020; Guan et al., 2020a; Zhou et al., 2020b). Therefore, nearly 308 million confirmed cases of COVID-19 have been recorded globally since the eruption of SARS-CoV-2 infection, including 5.49 million deaths as of 12th January

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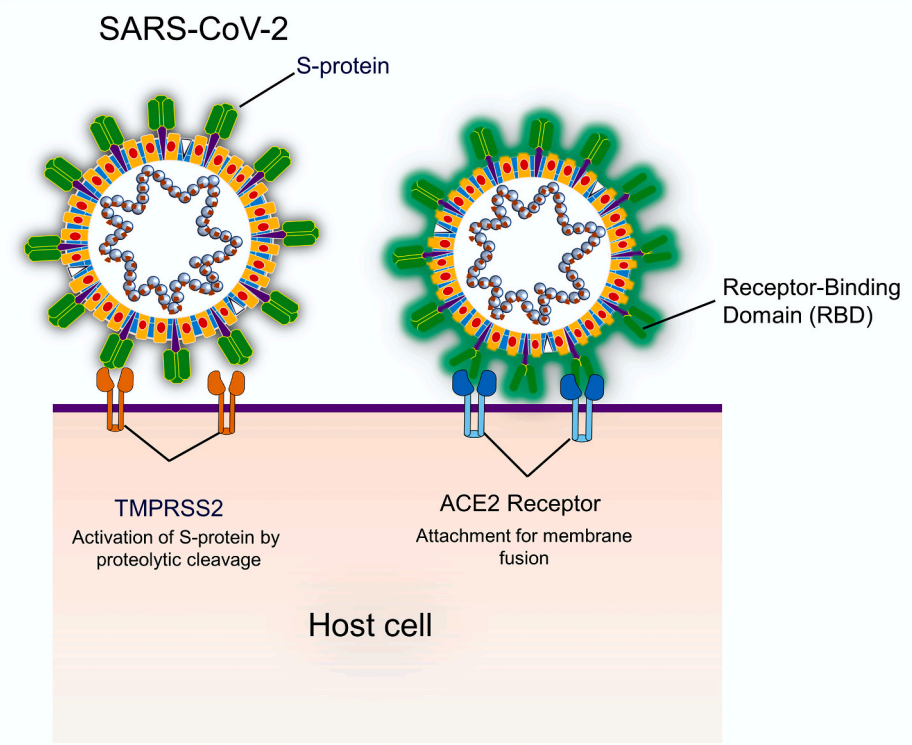

Fig. 1. Structural interactions between the glycosylated S-protein of SARS-CoV-2 with the membranal TMPRSS2 and ACE2 receptors on the target cell. TMPRSS2 instigate the activation of S-protein to expose receptor-binding domain (RBD) for the attachment with its functional receptor ACE2 for binding and fusion with the host cell.

2022 reported by WHO (WHO, 2022).

Like HCoV-NL63 and SARS-CoV, the membranal ACE2 protein — a zinc metalloprotease (carboxypeptidase), has been acknowledged as the most likely host cell receptor used by SARS-CoV-2 for causing COVID-19 (Baker et al., 2006; Zhou et al., 2020a). The ACE2 receptor is described as a homolog of ACE (angiotensin-converting enzyme) and for heterogeneous expression as a vital component in several tissues and organs to execute several cellular functions; for example, ACE2 functioned against the adverse consequences of RAS under various diseases (Patel et al., 2017; Santos et al., 2018). Of note, presentation of ACE2 receptor is minimum in the lungs, except highly expressed in specialized cells, i.e., type II pneumocytes, which are also known to express the TMPRSS2 (transmembrane protease serine 2) — functioned to activate the highly glycosylated spike protein (S-protein) of SARS-CoV-2 for binding with membranal ACE2 receptor to invade the host cell (Davidson et al., 2020) (Fig. 1). Besides, ACE2 presentation is not exclusive to the lungs; several tissues of other vital organs, including brain, nasal and oral mucosa, heart, vasculature, pancreas, gastrointestinal (GI) tract, and kidney, were reported for the ACE2 expression (Gembardt et al., 2005; Xu et al., 2020a). Under given conditions, the functional role of the ACE2 receptor that contributed to multi-organ damages by SARS-CoV-2 infection in COVID-19 patients remains elusive. Hence, to understand the essential contribution of ACE2 expression in SARS-CoV-2 invasion and pathogenesis, we have summarized the modus operandi adopted by SARS-CoV-2 via ACE2 receptor to root multi-organ damages in the host body along with corresponding clinical symptoms that can be useful in both the COVID-19 management and therapeutic development.

2. Role of ACE2 in SARS-CoV-2 infection

Typically, human coronaviruses (HCoVs) instigate the infection by attachment to the host cell via functional receptors (Fig. 1), which regulated the transmission, propagation, and clinical signs in the infected patients (Groneberg et al., 2005; Kuba et al., 2013; Xu et al., 2020b). Under SARS-CoV-2 infection, the ACE2 receptor has been established as the potent membranal receptor used by the virus for binding and entrance into the host cells via endocytosis or membrane fusion (Hoffmann et al., 2020; Ou et al., 2020; Wan et al., 2020). Notably, SARS-CoV-2 displayed the highly glycosylated homotrimeric S-protein (contained two subunits, i.e., S1 subunit-comprises receptor-binding domain (RBD) and S2 subunit aid the virus to fuse with the host cell membrane) on the envelope of the virus for binding to the host cell receptors (Xu et al., 2020b). Initially, a close association of the human ACE2 (hACE2) receptor with S-protein (RBD) of SARS-CoV-2 was elucidated using the computational molecular modeling approach (Xu et al., 2020b). Also, an experimental study on ACE2 expressing HeLa cell line found their vulnerability to SARS-CoV-2 invasion against ACE2 deficient cells, supporting the critical function of ACE2 receptor in SARS-CoV-2 invasion (Wan et al., 2020). Additionally, recombinant soluble hACE2 protein (rshACE2) was determined to dock with SARS-CoV-2 S-protein; thereby, demonstrated to act as a decoy to prevent the viral invasion into the cells and *in vitro* engineered human stem cell-organoids models (Monteil et al., 2020). According to the structural and biophysical studies, S-protein (binding via RBD region) of SARS-CoV-2 showed a 10 to 20 times higher binding attractions with the ACE2 receptor against SARS-CoV S-protein, suggested as a substantial factor for the elevated infectious performance of SARS-CoV-2 by comparison to SARS-CoV (Wrapp et al., 2020). Subsequently, the crystal structure of the ACE2-RBD complex was resolved, which displayed nearly identical binding modes of the ACE2-RBD-SARS-CoV-2 as in ACE2-RBD-SARS-CoV complex (Lan et al., 2020). Therefore, based on the reported sequence of experiments, the ACE2 receptor has been accepted as the primary functional protein required by SARS-CoV-2 to infect the host cells (Bian and Li, 2020).

Notably, the genetic material of HCoVs is highly susceptible to recurrent genetic recombination and directly linked with the origin of altered virulence (Hilgenfeld, 2014). A recent evaluation of more than 300,000 SARS-CoV-2 genomes demonstrated adaptive evolution that

Table 1
List of SARS-CoV-2 variants, emergence, and names of residual mutations in the RBD region of S-protein.

S. no.	SARS-CoV-2 Mutants	Designation			ACE2 binding (Yes/No)	RBD Mutations	Remarks
		Date	Classification	Origin			
1.	Alpha (B.1.1.7)	December 18, 2020 (WHO)	VOC	United Kingdom	Yes	N501Y	Due to N501Y mutation in RBD, Tyr^{501} exhibits additional interactions (Asp^{38}, Glu^{37}, Gln^{42}, and Tyr^{41}) and better affinity with ACE2 against WT-SARS-CoV-2 (Kim et al., 2021)
2.	Beta (B.1.351)	December 18, 2020 (WHO)	VOC	South Africa	Yes	N501Y K417N E484K	RBD contains N501Y mutation and shows additional molecular contacts with ACE2 (Gln^{42}, Tyr^{41}, and Asp^{38}), but K417N and E484K contribute to RBD interaction with His^{34}, Lys^{31}, and Asp^{30} residues, which weakens as they destabilize the RBD (Kim et al., 2021).
3.	Gamma (P.1)	January 11, 2020 (WHO)	VOC	Japan/ Brazil	Yes	N501Y K417T E484K	RBD carries K417T, E484K, N501Y. E484K, and K417T mutations, which contribute to an overall decrease in affinity against ACE2 receptor (Kim et al., 2021).
4.	Delta (B.1.617.2)	May 11, 2021 (WHO)	VOC	India	Yes	L452R T478K P681R	Delta variant contains L452R mutation as in RBD of Epsilon, but despite that Delta variant was reported with high infectivity and possess strong interaction with the ACE2 receptor due to an additional T478K mutation in RBD (Kim et al., 2021; Pascarella et al., 2021).
5.	Epsilon (B.1.427)	March 5, 2021 (WHO)	VOI	USA-California	Yes	L452R	L452R mutation in RBD leads to a reduction in length of ß-strands of Epsilon variant by almost 50% which destabilizes the RBD-ACE2 interaction interface. Due to unstable interface between RBD and ACE2, the Epsilon variant disengage from the ACE2 easily against WT- SARS-CoV-2 and other variants (Kim et al., 2021).
6.	Kappa (B.1.617.1)	April 4, 2021 (WHO)	VOI	India	Yes	L452R E484Q P681R	The interaction pattern of Kappa variant was found to be similar to Delta variant (Kim et al., 2021) but it is a strain of least concern than Delta mutant and lacks sufficient literature. However, E484Q is reported to destabilize the RBD of Kappa mutant and might be responsible to produce weaker interactions with ACE2 receptor (Pascarella et al., 2021).
7.	Omicron (B.1.1.529)	November 26, 2021 (WHO)	VOC	South Africa	Yes	G339D, S371L, S373P, S375F, K417N, N440K, G446S, S477N, T478K, E484A, Q493R, G496S, Q498R, N501Y, Y505H	Omicron mutant was classified immediately under VOC on 26 November 2021 after its first case reported on November 9, 2021(Control, 2021). On preliminary observation by the Technical Advisory Group on Virus Evolution, WHO, Omicron variant holds has a high risk of reinfection against other VOCs. This variant is considered as the most transmissible, immune escapable, and highly divergent by possessing a large number of mutations in the spike protein. N501 and Q498 mutations in RBD may increase the binding affinity to ACE2 receptor, whereas H655Y, N679K, and P681H mutations in non-RBD region of spike protein may enhance the spike cleavage, which may aid its transmission (Control, 2021).

primarily influences the nucleocapsid and multiple regions in the viral S-protein (Rochman et al., 2021). Thus, till this review, a total of seven SARS-CoV-2 mutants have been evolved and classified based on the mutation in the RBD region of the viral S-protein (Table 1). For instance, based on high infectivity, WHO has initially enlisted four SARS-CoV-2 mutants as variants of concern (VOC), viz. Alpha variant (B.1.1.7), Beta variant (B.1.351), Gamma variant (P.1), and Delta variant (B.1.617.2), whereas other two mutants were classified as variants of interest (VOI), named Epsilon variant (B.1.427) and Kappa variant (B.1.617.1), by November 2021. However, on 26 November 2021, WHO announced the advent of a new SARS-CoV-2 mutant called Omicron (B.1.1.529), which is directly classified under VOC due to its high transmission frequency and increased risk of infection (Control, 2021). Notably, both experimental and computational studies have deciphered the highly contagious characteristics of identified seven SARS-COV-2 mutants, suggested the function of favorable mutations in the RBD region to exhibit higher binding affinity with the hACE2 receptor (Harvey et al., 2021; Kim et al., 2021; Socher et al., 2021; Tian et al., 2021). For example, using steered molecular dynamics simulations and microscale thermophoresis analyses on the S-protein in SARS-CoV-2, Alpha, Gamma, Beta, and Delta variants were sequentially categorized for demonstrating stronger interactions with the hACE2 receptor followed by Kappa and Epsilon variants against the wild type (WT) strain of SARS-CoV-2 (Kim et al., 2021). Likewise, experimental analysis on S-protein of Omicron mutant showed its comparable binding affinity with the hACE2 receptor against WT strain, but weaker than the Delta variant (Wu et al., 2022). Besides, computational analysis of S-protein marks the Omicron with an advanced risk of immune evasion (Wu et al., 2022). The alterations in the RBD region of S-protein on the various variants of SARS-CoV-2 that contributed to an increase or decrease in binding affinity with the hACE2 receptor are summarized in Table 1.

2.1. *Molecular fate of ACE2 under SARS-CoV-2 invasion*

Recently, the assessment of SARS-CoV-2 reported that S-protein contributes to the downregulation of ACE2 expression on host cells via

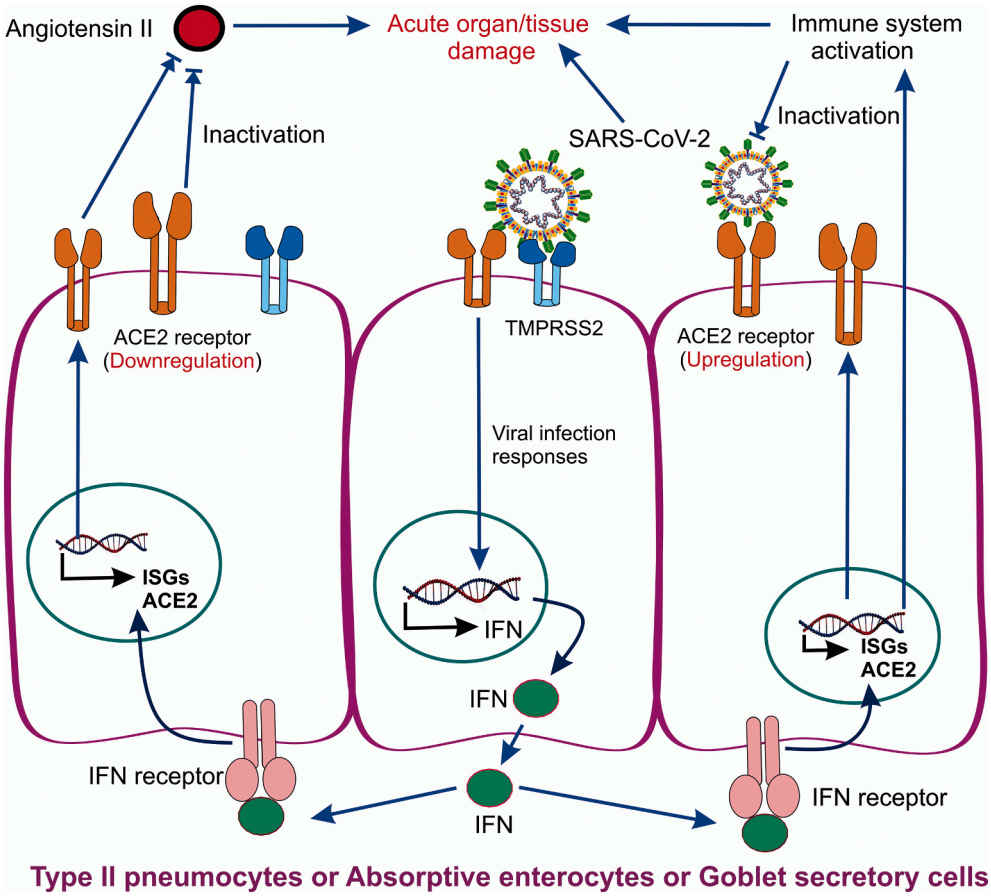

Fig. 2. A dubious position of interferon (IFN) in SARS-CoV-2 pathogenesis by augmenting the expression of membranal ACE2 receptor. The invasion of SARS-CoV-2 promotes IFN expression, which further activates the high expression of *AEC2* and canonical *ISGs* genes while ACE2 upregulation may promotes acute infection by SARS-CoV-2. Moreover, ACE2 assists to shield the host against acute organ or tissue damage via incapacitating the ang-II molecules. Meanwhile, generated ISGs signals may possibly trigger the broad immune reactions, which further promote the inhibition of infection caused by SARS-CoV-2 and acute lung injuries via augmenting the inflammatory responses.

ubiquitination in COVID-19 cases (Lei et al., 2021). Also, in virus-free analyses, *in vivo* treatment of virus-free S-protein plus acid-induced injury showed downregulation in mRNA expression and protein of ACE2 receptor (Yamaguchi et al., 2021). Hence, two modes for downregulation of ACE2 in COVID-19 cases have been advised: (i) direct virus attachment-intermediated ACE2 internalization/scaling (Wang et al., 2008) and (ii) lung injury/inflammation-mediated downregulation (Assiri et al., 2013; Imai et al., 2005; Yamaguchi et al., 2021). However, dose-dependent upregulation of ACE2 in human nasal epithelial cells was demonstrated by the interferons, i.e., IFN-γ or IFN-α2, where significant IFN-α2-driven ACE2 expression was noted at lower concentrations (0.1–0.5 ng/mL) (Ziegler et al., 2020). As S-protein assists in the ACE2-receptor-mediated internalization of SARS-CoV-2, the host IFN responses could, thus, stimulate the capability of the virus to preserve cellular targets expression in neighboring epithelial cells (Ziegler et al., 2020). Remarkably, screening of non-structural proteins plus structural proteins of SARS-CoV-2 supports the S-protein to facilitate the IFN-α effector, which further encourages the IFN-stimulated genes (ISGs) signaling and radically enhanced the production of long ACE2 protein in the bronchial epithelial cell line BEAS-2B (Zhou et al., 2021), as depicted in Fig. 2. Mechanistically, upregulation of long ACE2 protein was demonstrated with higher phosphorylation of signal transducer and activator of transcription 1 (STAT1) and STAT2 as a result of reinforcing their signaling with upstream Janus kinase, i.e., JAK1, by S-protein of SARS-CoV-2 to aid viral access in the bronchial epithelium (Zhou et al., 2021). Likewise, IFN-γ was noted to promote cellular differentiation into enterocytes expressing ACE2, supporting the high viral infection and replication (Heuberger et al., 2021). In another study, exposure to IFN-γ and IFN-λ caused a robust increment in the production of ISGs and ACE2 protein in nasal AE cells of infants (Salka et al., 2021). Meanwhile, internalization of virus-ACE2 complex and ACE2 degradation, resulting in the reduction of membranal ACE2 protein (Heyman et al., 2021). This results in augmented production of angiotensin II (Ang II) and causes reduced production of respective counter regulating angiotensin (1–7) molecules (Miesbach, 2020). Besides, ADAM-17 (shedase) activation by Ang II further contributes to the reduction in the membranal ACE2 receptor (Patel et al., 2014). Altogether, the depletion of ACE2 and Ang-(1–7) in the tissue causes inequality between the RAS and ACE2/angiotensin-(1–7)/MAS system (Nehme et al., 2019), in benefit of the ACE/Ang-II/AT1R (Angiotensin-II receptor type 1) pathway (Ni et al., 2020), which have been advised as a potential sponsor for multi-organ damages under COVID-19 pathogenesis (Heyman et al., 2021). This was likely demonstrated by the clinical symptoms of COVID-19 disease, including coagulopathy, oxidative stress, profound inflammation, tissue injury, and multi-organ dysfunctions (Gheblawi et al., 2020; Heyman et al., 2021). Of note, the ACE2 protein has been characterized as a vital tissue-protective factor in the course of severe lung injury (Imai et al., 2005; Kuba et al., 2005). Thereof, collective results established that SARS-CoV-2 targets the ACE2 receptor on host cells to increase the transduction via exploitation of species-specific interferon-driven overexpression of ACE2-mediated tissue-protective responses against SARS-CoV-2, which further promotes the viral invasion in the host cell (Ziegler et al., 2020). These assumptions were coherent with the observation that the expression of ACE2 in endothelial cells was augmented under acute COVID-19 as a corollary of the host's responses to viral infection (Klouda et al., 2021). Therefore, the feasible dual functions of IFNs during SARS-CoV-2 pathogenesis seek stringent supervision of infected individuals, those are under treatment using IFN as a therapeutic approach (Su and Jiang, 2020). (Fig. 2)

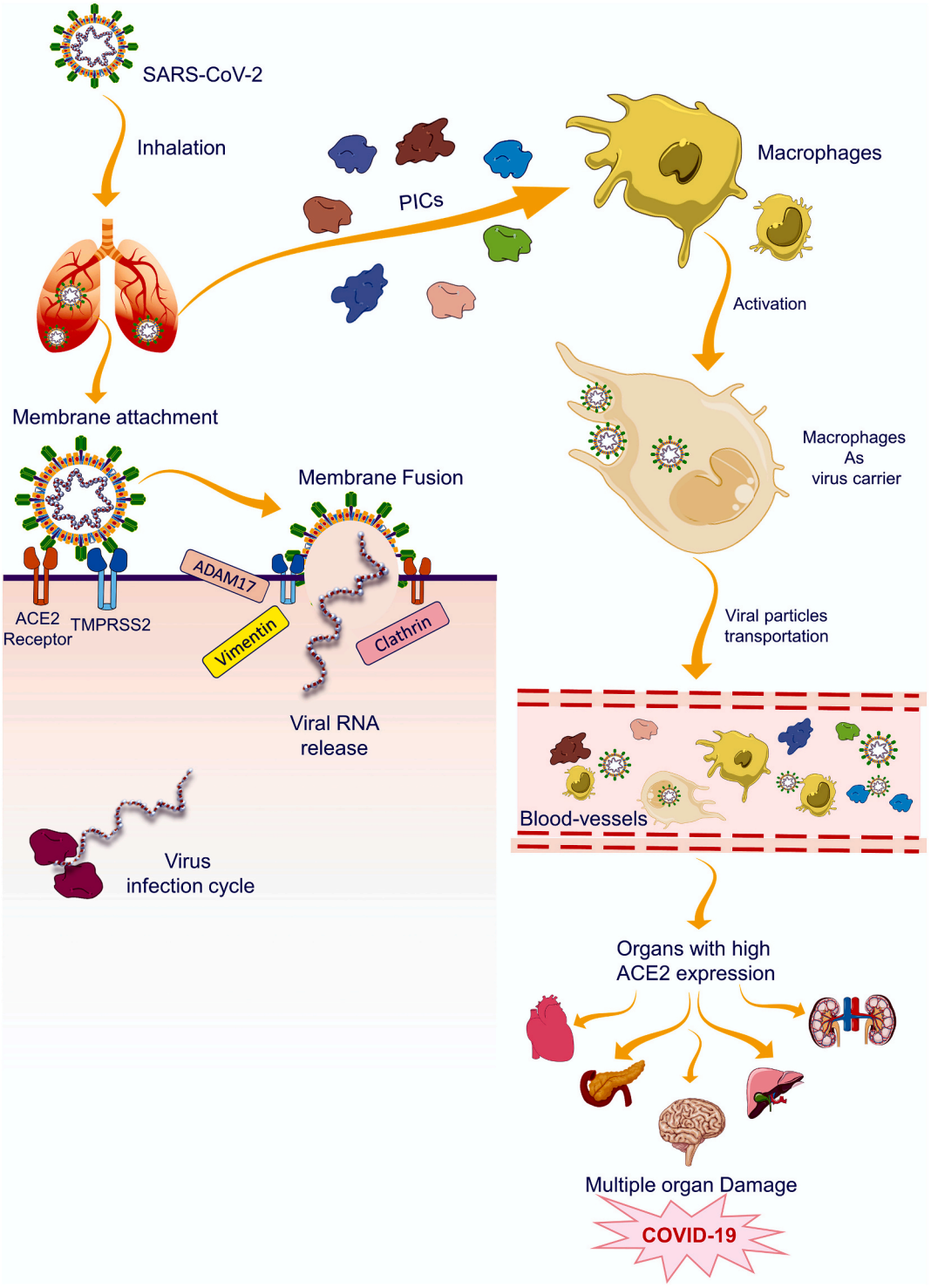

Fig. 3. Schematic of SARS-CoV-2 infection in the lungs followed by proliferation to other vital organs containing special cells with elevated expression of ACE2 receptor. At first, viral particles are assumed to invade the lungs and attack the cells expressing ACE2 receptors after activation of S-protein by membranal TMPRSS2 and other transmembrane proteinases like disintegrin metallopeptidase domain 17 (ADAM17) of the host, exploited by the virus to enter in the cells. In response to the viral entrance, virus-invaded cells along with the inflammatory cells generate PICs and chemokines that facilitate the inflammatory and immunological responses to halt the viral propagation. The cell-free viruses and the viruses phagocytosed by the macrophages situated in the blood are probably transported to other organs of the infected host body and characteristically distress the cells with elevated expression of ACE2 at resident sites (Ni et al., 2020).

3. Relationship of ACE2 with multi-organ injury in SARS-CoV-2 infection

Given that SARS-CoV and SARS-CoV-2 belonged to the same group and employed the common membranal ACE2 protein as a functional receptor on the host cells, convincing results from the sequence of investigation on SARS-CoV strain proposed that SARS-CoV-2 pathogenesis should be multiplex, comprising virus-induced inflammatory responses, extreme recruitment of inflammatory cells, auto-antibodies formation, expression of cytokines and chemokines, and altered

interferon responses (Gupta et al., 2020; Osuchowski et al., 2021; Parasher, 2021). For instance, considerable concentrations of chemokines plasma-like interleukin (IL-1, IL-6, IL-12, and IL-8), monocyte chemoattractant protein-1 (MCP-1), interferon-gamma-inducible protein 10 (IP-10), and pro-inflammatory cytokines (PICs) were examined in the plasma of infected populations by SARS-CoV (Wong et al., 2004). Besides, autopsy of SARS-affected individuals also supported the mentioned observations, where MCP-1 and PICs were distinguished remarkably in infected $ACE2^{+}$ cells by SARS-CoV by comparison to non-infected $ACE2^{+}$ cells, represented the substantial contribution of local immune-intermediated injury in response to the viral infection (He et al., 2006). Surprisingly, analogous promoted expression of PICs was also detected in the plasma of acute COVID-19 patients (Huang et al., 2020). Moreover, various findings acknowledged that the elevated expression of the membranal ACE2 induced by the onset of viral infection accelerates viral homing, but it was impaired by shedding and degradation during viral infection, which directed to Ang-(1–7) molecules depletion after infection; thereof, such events encouraged the overwhelming clinical symptoms of COVID-19 (Cao et al., 2020; Yan et al., 2021). Meanwhile, with the assumption that SARS-CoV-2 primarily targets the respiratory system, expression analysis of ACE2 protein based on stringent immunohistochemical tests suggested no or least ACE2 expression in a subtype of cells from the upper respiratory system (Hikmet et al., 2020). In contrast, under co-localization with mucin 1 $(MUC1)^{+}$ cells, ACE2 expression was demonstrated only within the type II pneumocytes of the lung (Lee et al., 2020); these results support the findings of ACE2 expression in type II pneumocytes predicted by single-cell RNA-sequencing (scRNA-seq) data analysis (Sungnak et al., 2020; Ziegler et al., 2020) and single antibody chromogenic staining method (Bertram et al., 2012; Hamming et al., 2004). Moreover, a concurrent Human Cell Atlas (HCA) Lung Biological Network analysis also detected the *TMPRSS2* and *ACE2* genes expression in other tissues enriched in nasal ciliated and goblet cells (Sungnak et al., 2020). For instance, the conceited expression of ACE2 was found in the eye, myocardial cells, placental trophoblasts, vasculature, male reproductive cells, ductal cells, bladder urothelial cells, enterocytes in the ileum region, and proximal tubule cells in the kidney (Hamming et al., 2004; Hikmet et al., 2020; Zhang et al., 2020a). Hence, given the substantial expression of ACE2 in several organs and as a receptor of SARS-CoV-2, the cell-free and phagocytosis-associated virus particles were suggested to travel through blood circulation to other susceptible organs of the host with the prominent display of ACE2 receptor (Fig. 3) (Ni et al., 2020). Consistent with it, multi-organ damages, such as acute lung and kidney injuries, heart injury, liver disease, and pneumothorax, were examined mostly in the severe SARS-CoV-2 infected individuals (Cheng et al., 2020; Shi et al., 2020a; Yan et al., 2021). Furthermore, the intestinal and other epithelia were stated for invasion by SARS-CoV-2 via active replication and *de novo* production of infective virus (Bwire et al., 2021; Wang et al., 2020a; Xiao et al., 2020). Therefore, initially pathogenesis of SARS-CoV-2 infection as COVID-19 was marked for severe respiratory disease only; however, later established that infected patients by SARS-CoV-2 can promptly continue to multi-organ dysfunction syndromes (MODS) (Fig. 3) (Lopes-Pacheco et al., 2021). Importantly, origin of SARS-CoV-2 infection in the human body before the induction of MODS is still remain elusive; thus, the downregulation of ACE2 was concluded as an indispensable reason for the initiation of multi-organ damages in SARS-CoV-2 acute infected populations.

4. Extrapulmonary manifestations in SARS-CoV-2 infection

Notably, SARS-CoV-2 infection occurs due to the activation and priming of its S-protein by the TMPRSS2 protein followed by the attachment to the membranal ACE2 protein on the host cells (Hoffmann et al., 2020). Successively, the excessive representation of ACE2 receptors on the different types of epithelial cells in the respiratory tract was classified for high susceptibility to infection by SARS-CoV-2 (Zhu et al., 2020a). However, despite being included in the initial targets, the manifestations related to the respiratory system, such as pneumonia and ARDS, were not always the primary symptoms and other comorbidities have been identified in severe COVID-19 disease, including prevalent hypertension (HTN), illness, obesity, diabetes mellitus (DM), and respiratory illness (Bian and Li, 2020; Kang et al., 2020; Shi et al., 2020b; Yang et al., 2020a). Moreover, cells expressing ACE2 protein in the intestinal epithelium, heart, kidney, vascular endothelium, lung (mostly type II alveolar cells), and smooth muscles; thus, such cells have been marked for invasion of SARS-CoV-2 that resulted in COVID-19 associated multi-organ failure or MODS (Lopes-Pacheco et al., 2021). Besides, the strong inflammatory responses caused by the viral infection in the lungs and other organs were suggested to cause multi-organ failure. For instance, upon entrance into the cells, SARS-CoV-2 stimulates T-lymphocytes, which elicits a strong immunological response as well as an inflammatory response. This results in the initiation of the inflammatory cascade and the generation of cytokines, including interferon-γ (IFN-γ), granulocyte-macrophage colony-stimulating factor (GM-CSF), interleukins (IL-1 and IL-6), and tumor necrosis factor-α (TNF-α), at an elevated rate than usual production under the phenomenon termed cytokine storm (CS), which ultimately leads to tissue damage (Shi et al., 2020b; Zhang et al., 2020b). Nevertheless, the exact cause of extrapulmonary symptoms is still obscure; however, several variables, including direct/indirect secondary damage by an inflammatory response generated against the invasion of the virus, have been suggested (Shi et al., 2020b; Zhang et al., 2020b).

4.1. Renal dysfunction

The incidence of acute kidney injury (AKI) in infected patients caused by SARS-CoV-2 varies amongst published research, ranging from 0.1 to 29% (Cummings et al., 2020; Farouk et al., 2020; Hirsch et al., 2020; Kunutsor and Laukkanen, 2020). For instance, research from China has reported that 25-29% of the deceased and acutely sick patients of COVID-19 were detected with AKI (Cheng et al., 2020; Lee et al., 2020). On the first day of admission, 34% of the patients had shown renal abnormalities, whereas 63% of all the patients developed proteinuria during the hospitalization (Adukia et al., 2020). Another research on COVID-19 demonstrated that 26.7% of patients showed symptoms of hematuria on admission while 44% of patients developed proteinuria and hematuria during hospitalization (Cheng et al., 2020). This was in accordance with the autopsy data, which advocated the endothelium damage in the kidney of infected patients and probably contributed to proteinuria (Varga et al., 2020). Also, the level of blood urea nitrogen (BUN) was noticed at around 27 and 66% in enduring and deceased COVID-19 patients, respectively (Cheng et al., 2020). Furthermore, recent findings elucidated that SARS-CoV-2 infected persons with a history of prolonged kidney diseases and hypertension are at greater risk for AKI (Guan et al., 2020b; Henry and Lippi, 2020). For instance, a recent study identified 32 COVID-19 patients with subclinical AKI displaying the high concentration of kidney tubular injuries (KTI) biomarkers, such as retinol-binding protein, N-acetyl-D-glycosaminidase, 1-microglobulin, and 2-microglobulin (Canatan et al., 2020; Sun et al., 2020a). Furthermore, assessments of post-mortem kidney samples from COVID-19 patient with AKI at stage 2 or 3 also revealed severe tubular damage as by far the most frequent finding in kidneys, typified by mainly moderate focal critical tubular necrosis (Golmai et al., 2020; Legrand et al., 2021; Santoriello et al., 2020; Schurink et al., 2020). These observations were coherent with the autopsy study of 6 patients with COVID-19, where microdissection of kidneys showed the presence of SARS-CoV-2, specifically enriched in the glomerulus (Puelles et al., 2020). Additionally, viral particles of SARS-CoV-2 were identified in the urine samples of COVID-19 patients (Sun et al., 2020b) — a discovery that either suggests the delivery of the virus from infested and broken renal tubular cells expressing ACE2 receptor (Li et al., 2003) or the separation of viral splits, as the higher molecular weight of SARS-

CoV-2 (600 kDa) should block it from being cleaned out of the integral glomerular filtration barrier (Yao et al., 2020a). Also, direct infection of podocytes and renal tubular epithelium by SARS-CoV-2 through ACE2-dependent pathway was associated with collapsing glomerulopathy, mitochondrial dysfunction, protein reabsorption vacuoles formation, acute tubular necrosis, and outflow of protein into Bowman's capsule (Larsen et al., 2020; Su et al., 2020). In support, RNA and protein of SARS-CoV-2 were identified during the assessment of infected kidneys using *in situ* hybridization with confocal microscopy (Puelles et al., 2020). Likewise, SARS-CoV-2 was identified in the renal endothelial cells, signifying viremia as a probable trigger of damage in endothelial tissue of the kidney and an apparent sponsor to AKI (Varga et al., 2020). Moreover, macrophage activation syndrome, endotheliitis, rhabdomyolysis, and advancement of microemboli and microthrombi in the context of hypercoagulability were also deciphered to promote AKI under SARS-CoV-2 infection (Varga et al., 2020; Zhang et al., 2020c). Thus, a substantial clinical characteristic of SARS-CoV-2-induced renal dysfunction implied that SARS-CoV-2 holds the potential to infect the kidney tissue; however, a direct role of the virus in the AKI development yet needs to be confirmed (Santoriello et al., 2020). Altogether, the mechanisms behind COVID-19 renal dysfunction remain uncertain and was suggested as a multifactorial mechanism with predisposing factors as an important contributor to AKI, including (i) direct association of virus trailed by the replication in the kidneys, ensuing in the imperfect renal function; (ii) local disturbance in renin-angiotensin-aldosterone system (RAAS) balance; (iii) dysregulation of SARS-CoV-2-interrelated immune retorts, specified by cytokine storm and lymphopenia, (iv) cardiovascular comorbidity and predisposing issues (e.g., nephrotoxins sepsis, and hypovolaemia) (Diao et al., 2021; Hirsch et al., 2020; Kunutsor and Laukkanen, 2020; Ronco et al., 2019; Ronco and Reis, 2020). Therefore, additional research is required to understand the pathophysiology behind renal dysfunction triggered by SARS-CoV-2, which will aid in the development of appropriate treatment options.

4.2. Gastrointestinal and hepatic dysfunctions

The COVID-19 cases have been increasingly documented with gastrointestinal (GI) and hepatic manifestations and may be associated with their worse outcomes (Chen et al., 2021a). Notably, abundant ACE2 and TMPRSS2 expressions were documented in the enterocytes of the colon and ileum in the intestines (Garland et al., 2021; Hamming et al., 2004). Besides, another study documented the modest subset of absorptive enterocytes and colon epithelial cells in the small intestine for the highest and moderate levels of ACE2 in the human body (Qi et al., 2020; Stanifer et al., 2020), which was consistent with the analysis of single-cell transcriptomics data supporting limited number of epithelial cells with ACE2 expression in the colon (Stanifer et al., 2020). Additionally, the vascular smooth muscle cells of the submucosa in the ileum and vascular endothelium were detected for the ACE2 receptor expression (Hamming et al., 2004). Together, the expression patterns of membranal ACE2 and TMPRSS2 proteins reflected the potential susceptibility of the intestine to SARS-CoV-2 infection. In this perspective, SARS-CoV-2 antigens were identified in the epithelial cells of the intestines, macrophages of the lamina propria, and lymphocytes (Qian et al., 2021). These interpretations were supported by the discovery of SARS-CoV-2 particles in the small intestinal epithelial cells collected from infected patients (88.23% of the total population) using immunofluorescence staining or electron microscopy (Livanos et al., 2021). Besides, high-dimensional assessments of tissues from the GI tract of infected individuals revealed modest degrees of inflammation, involving reduced frequencies of pro-inflammatory dendritic cells along with down-regulation of major inflammatory genes, such as *IL1B, CXCL2*, *CXCL8*, and *IFNG*, by comparison to the control population (Livanos et al., 2021); these findings marked the absence of a pro-inflammatory response even with the invasion of SARS-CoV-2 in the GI tract. Furthermore, the prevailing symptoms related to GI tract in COVID-19 patients were earlier described as nausea, diarrhea, vomiting, and abdominal discomfort (Garland et al., 2021). For instance, ~67% of infected individuals during the initial phase of infection caused by SARS-CoV or SARS-CoV-2 strain experienced diarrhea, but a considerable number of SARS-CoV-2 infected individuals additionally exhibited enteric dysfunctions (Kui et al., 2020; Leung et al., 2003). Also, in some COVID-19 cases, patients showed digestive system symptoms without appearing any respiratory symptoms while in a few cases, the GI symptoms, including GI bleeding, were reported that leading to discomfort in the respiratory system (Chen et al., 2021a; Huang et al., 2020). Therefore, this unusual presentation of GI symptoms has been suggested as a probable reason for the late diagnosis of COVID-19 (Zhang et al., 2020d) and considerable function of the GI tract in mitigating SARS-CoV-2–linked immune responses, including inflammation, need further assessment (Livanos et al., 2021).

Also, an increase in the percentage of COVID-19 patients who suffer from moderate to severe hepatic injury has been observed. Thus, experimental organoid models were used as an essential means to interpret the permissibility to SARS-CoV-2 in liver cell types. For example, designed human liver ductal organoids expressing TMPRSS2 and ACE2 receptors were demonstrated to recapitulate SARS-CoV-2 replication, indicating the susceptibility of epithelium in the bile duct for virus invasion and resulting in direct cholangiocyte injury and subsequent bile acid accumulation (Zhao et al., 2020). Likewise, human pluripotent stem cell-derived liver organoids containing particularly hepatocytes with albumin were also demonstrated for ACE2 expression and infiltration of SARS-CoV-2 pseudoparticle (Yang et al., 2020b). In support, post-mortem analysis of liver tissue from acute COVID-19 patients using electron microscopy reveals possible coronavirus-like nanobodies in the cytoplasm of hepatocytes along with swelling in mitochondria and apoptosis (Wang et al., 2020b). Conversely, an in-depth proteomic evaluation of autopsy tissue from COVID-19 patients (19 individuals) showed little indication for the dynamic SARS-CoV-2 replication in the liver (Nie et al., 2021). Besides, hepatic protein signatures suggested the upregulation of profibrotic pathways, dysregulation of fatty acid oxidation and oxidative phosphorylation, and immune activation; such variations in the proteomic display can be linked with the manifestation of coagulative hepatocyte necrosis and hepatic steatosis (Nie et al., 2021). Moreover, the patients with persistent liver infections, especially with pre-existing cirrhosis, were marked for horrendous consequences in COVID-19 and connected to respective immunocompromised conditions (Zhang et al., 2020d). Therefore, the liver lesions have been marked as minor and transitory conditions, but remarkable damage may occur in the liver of severely SARS-CoV-2 infected individuals under poor prognosis (Chaibi et al., 2021). In addition, several reports have described hepatotoxicity in COVID-19 patients as drug-induced liver injury (DILI) (Sodeifian et al., 2021). For instance, DILI was noted to enhance the expression of liver enzymes by several medications, such as hydroxychloroquine and remdesivir, used in the treatment of SARS-CoV-2 infection (Sodeifian et al., 2021). Therefore, a conclusive mechanism for liver injury in COVID-19 is still obscure, and further *in vivo* research is required on SARS-CoV-2 induced damage in the liver.

4.3. Cardiac manifestation

Cardiovascular arrhythmias or heart failure may worsen during COVID-19 and it can also be enhanced by shock along with or without hemodynamic instability (Zhu et al., 2020a). Such cardiovascular complications are considered as delayed complications in infected individuals, which may appear suddenly during hospitalization or even after improvement in their respiratory health (Fried et al., 2020; Lang et al., 2020). Therefore, the onset of acute cardiovascular injury caused by COVID-19 has been linked with an absolute poor prognosis (Giustino et al., 2020; Labbe et al., 2021). For instance, COVID-19 individuals diagnosed with cardiac injury were noted for a high ranking of mortality

(51.2-59.6%) by comparison to the patients with no cardiac injury (4.5%-8.9%) during hospitalization (Guo et al., 2020; Shi et al., 2020a). Nevertheless, clinical data suggested that the vulnerability and consequences of COVID-19 were effectively connected to cardiovascular diseases (CVD), such as arrhythmias, myocardial injury, venous thromboembolism, and acute coronary syndrome (ACS) (Nishiga et al., 2020). A recent analysis based on single-cell RNA sequencing reported that myocardial cells (more than 7.5%) showed a high presentation of ACE2 protein (Zou et al., 2020), which may accelerate the incursion of SARS-CoV-2 into cardiomyocytes and initiate immediate cardiotoxicity. In support, some cases of COVID-19 were detected for the occurrence of SARS-CoV-2 particles in the cardiac tissue by reverse transcription-polymerase chain reaction (RT-PCR) (Yao et al., 2020b), indicating that direct cardiotoxicity may induce by SARS-CoV-2 infection. Such assumptions were further supported by *in vitro* studies demonstrating the efficient infection and replication of SARS-CoV-2 in human pluripotent stem cell-derived cardiomyocytes (hPSC-CMs) expressing ACE2 receptor (Bailey et al., 2021; Marchiano et al., 2021; Perez-Bermejo et al., 2021). Of note, infected hPSC-CMs were also characterized for cessation of beating (Sharma et al., 2020), compromised electrophysiological function (Marchiano et al., 2021), transcriptional and morphological signatures of damage (Perez-Bermejo et al., 2021), impaired contractile function (Bailey et al., 2021; Marchiano et al., 2021), and cell death (Bailey et al., 2021; Marchiano et al., 2021). Furthermore, autopsy and endomyocardial biopsy specimens' analysis of 4 cases with COVID-19 highlights the presence of SARS-CoV-2 protein in cardiomyocytes but not in cardiac fibroblasts, macrophages, or endothelial cells (Bailey et al., 2021). Likewise, among the autopsies of 39 cases of COVID-19, RNA of SARS-CoV-2 was identified in the myocardium of 24 patients while only negative-sense RNA, which indicates the active replication of SARS-CoV-2, was discovered in the myocardium of 5 patients suffering from the highest viral load (Lindner et al., 2020). In another autopsy report of 41 COVID-19 cases, 30 cases showed the manifestation of SARS-CoV-2 RNA in the heart while the myocardium contained the least number of cells infected by SARS-CoV-2 (Bearse et al., 2021). In contrast, no viral antigens were identified in the heart amongst autopsy specimens from five COVID-19 patients, but all the patients were diagnosed with acute myofibrillar anomalies (Bailey et al., 2021). Likewise, post-mortem analysis of all 8 patients with COVID-19 showed no mark of SARS-CoV-2 particles in the heart detected by immunohistochemistry, *in situ* hybridization, or qRT-PCR approach (Massoth et al., 2021). Thus, the involvement of direct invasion of SARS-CoV-2 in cardiomyocytes to *in vivo* pathogenesis remains unclear. Under another perspective for cardiac manifestations produce in COVID-19, SARS-CoV-2 has been described to initiate a systemic immune response, including activation of inflammatory pathways, and was suspected to promote the myocardial injury in SARS-CoV-2 infected population (Huang et al., 2020). For example, pro-inflammatory cytokines, like TNF-α, IL-1, and IL-6, were suggested to produce a negative inotropic effect on cardiac contractility in COVID-19 patients (Li et al., 2021a). Meanwhile, TNF-α was deduced to produce a constant stimulation of inflammatory signalling to trigger extensive cardiomyocyte programmed cell death, resulting in pathological remodelling of the left ventricle; and eventually, leading to acute heart failure (Li et al., 2021a). Thus, under SARS-CoV-2 infection, virus-induced hyper inflammation with cytokine discharge can result in direct myocardial suppression and inflammation, plaque instability, hypercoagulable state, and vascular inflammation (Prabhu, 2004). Therefore, biomarkers related to inflammation along with cardiac troponins, fibrinogen, D-dimer, and natriuretic peptides have been suggested for concurrent examination (Canatan et al., 2020). Collectively, COVID-19 cardiovascular syndrome must be managed by a multidisciplinary approach involving cardiologists, intensive supervision, and infectious disease specialist.

4.4. Neurological findings

A variety of neurological problems have been documented in individuals diagnosed with COVID-19, suggesting that SARS-CoV-2 can induce damage both in the central and peripheral nervous systems (Liu et al., 2021). Therefore, extensive analysis of neuropathology in individuals with COVID-19 was suggested due to direct neuroinvasion by SARS-CoV-2 or indirectly by peripheral infection coupled with virus-induced immune responses (Iadecola et al., 2020). Thus, considerable interest has been centered on the neuroinvasion of SARS-CoV-2, which has returned contradictory conclusions (Cantuti-Castelvetri et al., 2020; Jacob et al., 2020; Matschke et al., 2020; Meinhardt et al., 2021; Pellegrini et al., 2020; Song et al., 2021). For instance, systematic analysis of the brain showed no molecular marks for the incursion of SARS-CoV-2, but distinctive cellular perturbations were observed, demonstrating that cell barrier of the choroid plexus sense and assist in the transmission of induced peripheral inflammation to the brain, and also aid the infiltration of peripheral T cell into the parenchyma (Yang et al., 2021). Moreover, microglia and astrocyte subpopulations were noticed for association with COVID-19 that reveal pathological characteristics of the cell as previously studied in human neurodegenerative disease (Frigerio et al., 2019; Keren-Shaul et al., 2017). Meanwhile, the viral genome of SARS-CoV-2 was found in the cerebrospinal fluid (CSF) and in the brain of some COVID-19 cases, encouraging the supposed neuroinvasion by SARS-CoV-2 (Iadecola et al., 2020; Paniz-Mondolfi et al., 2020; Puelles et al., 2020). Besides, viral RNA and proteins or virus-like nanobodies were identified in the blood and brain endothelial cells, respectively (Andersson et al., 2020; Cantuti-Castelvetri et al., 2020; Paniz-Mondolfi et al., 2020; Song et al., 2021), implying neuroinvasion of SARS-CoV-2 via the hematogenous channel. Also, SARS-CoV-2 infection in the pericyte underlies the invasion of the virus into the restricted central nervous system (CNS) space as well as neurological symptomatology because of inflammation in perivascular spaces and compromised local blood–brain barrier (BBB) (Bocci et al., 2021). For instance, magnetic resonance imaging in COVID-19 patients demonstrated the formation of lesions that was consistent with a cerebral small-vessel disorder and BBB disruption (Conklin et al., 2021; Conte et al., 2020; Radmanesh et al., 2020). This interpretation was in accordance with the autopsy studies (Conklin et al., 2021; Matschke et al., 2020; Reichard et al., 2020). In the infected brains of humans and animal models, enhanced production of empty basement membrane tubes — also named string vessels, indicating the remains of lost capillaries, which proved that SARS-CoV-2 main protease (M^{pro}) holds the potential to digest the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) essential modulator (NEMO) — an essential regulator of NF-κB; hence, highlights the viral infection in the endothelial cells of the brain (Wenzel et al., 2021). Collectively, the reported studies indicate virus-induced damages both in the peripheral and central nervous systems of COVID-19 patients. Also, more than 35% of COVID-19 individuals were noted for the development of neurological symptoms as the condition progresses. For instance, COVID-19 patients presented both peripheral neurological manifestations (PNM), including skeletal muscle damage, complete or partial loss of smell (anosmia) and taste (ageusia), Guillain Barrè syndrome (GBS), and central neurological manifestations (CNM), which comprises headache, dizziness, acute transverse myelitis, encephalopathy, acute hemorrhagic necrotizing encephalopathy, and cerebrovascular accident (Ahmad and Rathore, 2020; Filatov et al., 2020). However, the cause of such complications is still unclear, whether they are directly related to the hypoxic metabolic changes, viral infection or, post-infection auto-immune reactions (Ahmad and Rathore, 2020; Filatov et al., 2020).

4.4.1. Central nervous system manifestations

The prevailing central nervous system (CNS) symptoms, including dizziness and headache in 16.8 and 13.1% cases, respectively while the rare symptoms such as ataxia, consciousness, seizure, cerebrovascular

Box 1

SARS-CoV-2 induced organ specific manifestations and linked symptoms.

Organ specific manifestations in SARS-CoV-2 infection	Remarks
Pulmonary infection	• Mild symptoms included infection in the upper respiratory tract accompanied by coughing and sore throat. • Moderate symptoms include fever along with pneumonia and occasionally silent pneumonia with silent hypoxia. • Severe symptoms include acute respiratory distress syndrome (ARDS) in the second week of infection followed by respiratory failure and death.
Renal dysfunction infection	• Elevated markers of proteinuria, hematuria, blood urea nitrogen (BUN), and creatinine in the serum during hospitalization. • These symptoms worsened into acute kidney injury (AKI) and consequently resulted into death.
Gastrointestinal infection	• Anorexia, diarrhea, nausea, vomiting, and abdominal pain in 3-79% of cases.
Hepatic Infection	• Elevated alanine aminotransferase (ALT), aspartate aminotransferase (AST), and bilirubin. • Hypoproteinemia and acute hepatic injury. • In acute infection, mild to moderate elevation in the serum transaminase and lactate dehydrogenase (LDH) level.
Cardiovascular infection	• Heart failure, acute cardiac injury, myocarditis, acute coronary syndrome, arrhythmia, and thromboembolism. • Heart failure as common dysfunction due to pre-exiting medical comorbidities such as diabetes, coronary artery disease, and hypertension. • Common symptoms linked with cardiac infection involves arrhythmias and sudden cardiac arrest caused by heart palpitation along with ventricular tachycardia and fibrillation, but it is still poorly understood.
Central nervous system infection	• Headache, dizziness, ataxia, impaired consciousness, seizures, acute cerebrovascular problems, cerebral hemorrhage, acute ischemic stroke, encephalitis, and encephalomyelitis. • Loss of smell (olfactory), and taste.
Peripheral nervous system infection	• Other symptoms included facial palsy/Bell's palsy, Guillain-Barré syndrome, and Miller-Fisher syndrome.
Hematological infection	• Cytopenia: lymphopenia, neutrophilia, mild thrombocytopenia, and monocytopenia. • High level of LDH and ferritin, and hemophagocytosis. • Low level of blood clotting proteins due to excessive cytopenia results in coagulopathy.
Skin infection	• Urticarial and maculopapular lesions, where urticarial lesions are considered as a diagnostic sign for COVID-19 whereas maculopapular lesions indicate acute COVID-19. • Other frequent skin manifestations include chilblain-like lesions, especially localized on fingers and toes. • Least common symptoms include vesicular, purpura, livedoid eruption, and papulovesicular lesions.
Reproductive system infection	• In females, enduring with polycystic ovary syndrome (POCS) was found more susceptible to SARS-CoV-2 infection. • Damage in ovaries and imbalance in reproductive hormones were marked for altered reproductive system functions. • Vertical transmission of COVID-19 from a pregnant mother to the newborn child has also been reported. • In males, congestion, red blood cell exudation in testes, interstitial edema, and epididymitis as well as thinning of seminiferous tubules and impaired spermatogenesis was noted as post effects of COVID-19.
Ophthalmic infection	• Epiphora, conjunctivitis, redness, hyperemia, eyelid edema, dryness, swelling, itching, and episcleritis were observed. • Ophthalmic manifestations in COVID-19 patients were observed in the different periods: (i) Acute (1 to 7 days): acute retinal necrosis, optic neuritis, Miller Fisher syndrome, orbital cellulitis, and dacryoadenitis. (ii) Subacute (7 to 20 days): vitritis, and pseudomembranous hemorrhagic conjunctivitis (iii) Delayed (after 20 days): Blepharitis, Serpiginous choroiditis, papillophlebitis, and neurogenic ptosis. Also. two symptoms (central retinal vein occlusion and rhino-orbito-cerebral mucormycosis) were observed along with the acute, subacute, and delayed symptoms.
Endocrine infection	• Impaired level of thyroid-stimulating hormone (TSH), and triiodothyronine (T3). • Other endocrine manifestations include thyrotoxicosis, adrenal dysfunction, adrenal insufficiency, and acute adrenal infarction.

disease, nerve pain, and vision impairment in 0.5, 7.5, 0.5, 2.8, 2.7, and 1.4% cases, respectively were documented in the COVID-19 patients. Moreover, symptoms such as malaise, headache, and myalgia were commonly noted in the early stages of neurological syndromes while under severe COVID-19 cases, altered sensorium was also observed that results in confusion, delirium, and stupor followed by coma as the final stage, detailed reviewed elsewhere (Ahmad and Rathore, 2020). Therefore, patients enduring acute COVID-19 have been marked for a greater incidence of neurological signs and symptoms, which may be attributed to cerebral hypoxia triggered by respiratory failure (Ahmad and Rathore, 2020).

4.4.2. Peripheral nervous system manifestations

The remarkable symptoms of the peripheral nervous system (PNS) in COVID-19 patients included hyposmia, anosmia, hypogeusia, ageusia, GBS, and muscular soreness while a rare incidence for spinal cord involvement was also reported (Mao et al., 2020). Also, anosmia and/or ageusia were studied as the most prevalent PNS symptoms in SARS-CoV-2 infection. For instance, in a European study, the olfactory dysfunctions and/or gustatory dysfunctions were observed in 85.6 and 88.0%, respectively among mild to moderate enduring COVID-19 patients. However, the prevalence of infection was higher in women, including 44% of cases displayed early olfactory recovery while the symptoms resist for up to 14 days before full recovery (Lechien et al., 2020). Of note, olfactory symptoms were noted for sudden appearance accompanied by less severe nasal symptoms, including nasal obstruction or immoderate nasal discharge (Lechien et al., 2020). Moreover, the occurrence of ageusia and anosmia were noted in most of the individuals without any other symptoms (Mao et al., 2020).

4.5. Hematological dysfunction

Recent studies on COVID-19 pathogenesis have shown hypersensitivity pneumonitis instead of viral pneumonia (Kui et al., 2020). Besides, SARS-CoV-2 has been documented to cause a hyperactive immune response, commonly referred to as cytokine storm (CS) in COVID-19 patients. Thus, the most serious consequence of pneumonia in COVID-19 patients was the failure of multi-organs, which was linked with an excessive release of pro-inflammatory cytokines and a decrease in the oxygenation capacity of the patient's blood. Several other consequences were also detailed in acute COVID-19 cases such as coagulation dysfunction and septic shock along with the difficulty in correcting metabolic acidosis (Kui et al., 2020; Lin et al., 2020; Rothan and Byrareddy, 2020). Furthermore, the early onset of COVID-19 was frequently noted with normal/reduced white blood cells (WBC) count or reduced level of lymphocyte (lymphopenia) (Kui et al., 2020; Lin et al., 2020; Rothan and Byrareddy, 2020; Wang et al., 2020c). In this context, COVID-19 patients enduring thrombocytopenia were observed with epistaxis, lower-extremity purpura, and neurological manifestations, such as headache, suggested due to subarachnoid microhemorrhage in the brain detected by computed tomography (CT) (Zulfiqar et al., 2020).

4.6. Skin manifestations

According to recent research, infection instigated by SARS-CoV-2 might result in cutaneous involvement in enduring patients with severe COVID-19 (Behzad et al., 2020). For instance, a study on 88 patients showed that generalized urticaria, erythematous rash, and chickenpox-like blisters were the main skin manifestations under COVID-19 while observed skin lesions were mildly irritating and mainly observed in the trunk of the body (Recalcati, 2020).

4.7. Reproductive system dysfunction

Although high expression of ACE2 has been documented in the male reproductive system by comparison to the female's, thus, growing evidence have indicated that reproductive systems in human can be infested by SARS-CoV-2 (Guo et al., 2021; Jing et al., 2020). For instance, in females, gonadotropin-dependent presentation of ACE2 receptor has been reported in ovaries (Pan et al., 2013; Reis et al., 2011); hence, SARS-CoV-2 was suggested to inflict adverse effects on the female reproductive system (Jing et al., 2020). In this context, female patients infected by SARS-CoV-2 were noted for ovarian damage, including deteriorated ovarian reserve and reproductive endocrine disorder (Ding et al., 2021). Moreover, the presence of SARS-CoV-2 was also detected in vaginal swabs (Barber et al., 2021; Schwartz et al., 2021; Scorzolini et al., 2020); however, the general impact of SARS-CoV-2 infection on the female reproductive system and function remained unclear (Chen et al., 2021b).

Meanwhile, in males, a study using single-cell RNA sequencing claimed that the ACE2, which is expressed in Leydig cells, germ cells, and Sertoli cells in the testis, can be infected by SARS-CoV-2 (Shen et al., 2020), suggested the testicular tissue as a reservoir as well as tropism site for SARS-CoV-2 (Guo et al., 2021). In this context, male patients were studied with low sperm count along with reduced sperm motility as post-infection consequences of COVID-19, which continued for up to three months (Guan et al., 2020b). Also, male patients were reported with congestion, red blood cell exudation in testes, interstitial edema, and epididymitis as well as thinning of seminiferous tubules post-COVID-19 infection, suggested impaired spermatogenesis as a consequence of COVID-19 in male patients (Li et al., 2020). Therefore, recovered male patients were advised for the semen examination as well as testicular and reproductive functions. Further, external genital pain was also reported in rare cases of COVID-19 in male patients (Özveri et al., 2020). However, the process by which SARS-CoV-2 invaded the reproductive system in humans remains elusive.

4.8. Ophthalmic manifestations

Under COVID-19, high chances for the ocular manifestations have been suggested in the form of local or transitory vasculitis due to the ACE2 expression on endothelial cells and enhanced vascularity of conjunctiva (Gu and Korteweg, 2007; Ho et al., 2020). Thus, SARS-CoV-2 was detected to cause a wide range of ophthalmic symptoms, including conjunctivitis, anterior uveitis, retinitis, and optic neuritis (Ulhaq and Soraya, 2020; Wu et al., 2020; Zou et al., 2020). Of note, 2 to 32% of prevailing symptoms in ocular functions were related to COVID-19 severity (Khavandi et al., 2020; Wu et al., 2020; Zou et al., 2020). Thus, similarly, to other non-respiratory systems, infected patients may incur ophthalmic symptoms as the initial symptom of COVID-19 in the absence of any other dysfunction. Also, the lacrimal gland was advised to play a functional role in the hematogenous distribution of the virus along with several other pathways, which may be involved in the transmission of the virus from the ocular to the respiratory tract and vice versa through the nasolacrimal system (Canatan et al., 2020). Thus, like other respiratory viruses, SARS-CoV-2 is likely to exhibit an ocular tropism in the COVID-19 patients.

4.9. Endocrinal manifestations

The association between blood sugar level and respiratory illnesses is widely known (Baker et al., 2006). The COVID-19 is being connected with an increment in blood sugar levels among diabetics' people experiencing poor control (Zhu et al., 2020b). For example, research studies suggested that greater than 50% of all confirmed or probable COVID-19 patients had an increased levels of blood sugar (hyperglycemia) and approximately 33% of patients were suffering from diabetic ketoacidosis (Thaweerat, 2020). There are possibilities that SARS-CoV-2 directly affects the pancreas; since, the pancreas exhibit enhanced expression of ACE2 receptor along with the inflammatory responses that may direct to pancreatic failure in severe COVID-19 patients (Thaweerat, 2020). Moreover, these consequences were also associated with the elevated

Table 2
List of COVID-19 vaccines approved for use in human available under EUA and WHO emergency use.

Drug/Vaccines	Type	Administration	Status	Age	Dose	Efficacy	Developed by	References
Pfizer-BioNTech COVID-19 Vaccine (Comirnaty)/ BNT162b2	mRNA based	Shot in the muscle of the upper arm	FDA approved	>16 (under FDA approval) 12-15 (under EUA guidelines)	Two doses on three weeks interval	>90% efficacy	Pfizer, Inc., and BioNTech	(CDC, Centers for Disease Control and Prevention. Atlanta; GA: US Department of Health and Human Services; Division of Cancer Prevention and Control., 2021; Dagan et al., 2021; FDA, 2021a; Tartof et al., 2021)
Janssen COVID-19/Johnson & Johnson vaccine/Ad26. COV2.S	Adenovirus type 26 based delivery of spike protein encoding gene	intramuscular injection	Available under EUA only and approved under WHO emergency use in 85 countries	>18	Single Dose	66- 85% effective in moderate to severe COVID-19 occurring at least 28 days of infection	Janssen Biotech Inc., a Janssen Pharmaceutical Company of Johnson & Johnson	(Administration, 2021; Emary et al., 2021; FDA, 2021b)
Moderna COVID-19 Vaccine/ mRNA-1273/ Spikevax	mRNA	Shot in the muscle of the upper arm	Available under EUA only and approved under WHO emergency use in 78 countries	>18	2 shots, 28 days apart	94%	ModernaTX, Inc.	(CDC, 2021; FDA, 2021a; WHO, 2021a)
Vaxzervria/ ChAdOx1 nCoV-19/ AZD1222/ Covishield	Non-replicating viral vector	Intramuscular	Available under EUA only and Approved under WHO emergency use of Vaxzervria in 127 countries and Covishield in 47 countries	>18	2 doses on 14 days apart	66.7%	Oxford and AstraZeneca	(Asano et al., 2022; COVID19, 2021)
Sputnik V	Recombinant adenovirus vaccine (rAd26 and rAd5)	intramuscularly	Approved under WHO emergency use	>18	2 doses on 2 days apart	80%-90%	Gamaleya Research Institute, Acellena Contract Drug Research and Development, Russia	(Logunov et al., 2021; Nogrady, 2021)
Sputnik Light	Recombinant adenovirus vaccine (rAd26)	intramuscular injection	Approved under WHO emergency use	>18	Single Dose	~70%	Gamaleya Research Institute, Acellena Contract Drug Research and Development, Russia	(clinicaltrials.gov, 2021a; Tukhvatulin et al., 2021)
CoronaVac	Inactivated vaccine (formalin with alum adjuvant)	intramuscular injection	Approved under WHO emergency use in 46 countries	3 -17 Years	2 doses on 28 days apart	100%	Sinovac Research and Development Co., Ltd.	(COVID19, 2021; Han et al., 2021; WHO, 2021b, 2021c)
BBIBP-CorV/ Covilo	Inactivated vaccine	intramuscular injection	Approved under WHO emergency use in 72 countries	3 Years to 17 Years	Three doses apart 28 days	78%	G42 Healthcare	(COVID19, 2021; Kozlovskaya et al., 2021; Xia et al., 2021)
EpiVacCorona	Peptide vaccine	intramuscular injection	Approved under WHO emergency use in 2 countries (Russia and Turkmenistan)	>18	2 doses	-	Federal Budgetary Research Institution, Russia	(clinicaltrials.gov, 2021b; COVID19, 2021)
Convidecia/Ad5-nCoV	Recombinant vaccine (adenovirus type 5 vector)	intramuscular injection	Approved under WHO emergency use in 10 countries	>18	Single Dose		CanSino Biologics, China	(CanSino, Biologics Inc., 2021; Li et al., 2021b)
Covaxin (BBV152)	Inactivated vaccine	intramuscular injection	Approved under WHO emergency use in 12 countries	>18	2 doses apart of 4 weeks	77%	Bharat Biotech, ICMR; Ocugen; ViroVax, India	(COVID19, 2021; Desai et al., 2021; Ella et al., 2021; Group et al., 2021; Kozlovskaya et al., 2021)
WIBP-CorV	Inactivated vaccine	intramuscular injection	Approved under WHO emergency use in 2 countries (China and Philippines)	>18	2 doses of 21 to 28 days apart	79%	Wuhan Institute of Biological Products; China National Pharmaceutical Group (Sinopharm), China	(COVID19, 2021; Explainer, 2021)
KoviVac/ CoviVac	Inactivated vaccine	intramuscular injection	Approved under WHO emergency use only in Russia	>18	2 doses of 21 to 28 days apart	-	Chumakov Federal Scientific Center for Research and Development of	(Russian, Federation, 2021)

(*continued on next page*)

Table 2 (*continued*)

Drug/Vaccines	Type	Administration	Status	Age	Dose	Efficacy	Developed by	References
							Immune and Biological Products, Russia	
ZF2001/RBD-Dimer/ ZIFIVAX	Recombinant protein subunit vaccine	intramuscular injection	Approved under WHO emergency use in 3 countries (China, Indonesia, Uzbekistan)	>18	3 doses over a period of 3 months	82%	Anhui Zhifei Longcom Biopharmaceutical, Institute of Microbiology of the Chinese Academy of Sciences	(COVID19, 2021)
QazVac (QazCovid-in)	Inactivated vaccine	intramuscular injection	Approved under WHO emergency use in 2 countries (Kazakhstan, Kyrgyzstan)	>18	2 doses on 21 days apart	-	Research Institute for Biological Safety Problems, Kazakhstan	(Zakarya et al., 2021; Zhugunissov et al., 2021)
COVIran/ Barekat	Inactivated vaccine	intramuscular injection	Approved under WHO emergency use only in Iran	>18	2 doses on 28 days apart	~90%	Shifa Pharmed Industrial Group, Iran	(Abdoli et al., 2021; COVID19, 2021; Hosseinpour, 2021)
Abdala (CIGB 66)	Protein subunit vaccine	intramuscular injection	Approved under WHO emergency use in 4 countries	>18	3 doses on 2 weeks apart	92.28%	Center for Genetic Engineering and Biotechnology, Cuba	(COVID19, 2021; RPCEC, 2021)
Soberana 02/ Soberana Plus	Protein subunit Vaccine	intramuscular injection	Approved under WHO emergency use only in Cuba	>18	3 doses on 28 days apart	92.4%	Finlay Institute of Vaccines; Pasteur Institute, Cuba, Iran	(Chang-Monteagudo et al., 2021; COVID19, 2021; Toledo-Romani et al., 2021)
MVC-COV1901	Protein subunit vaccine	intramuscular injection	Approved under WHO emergency use only in Taiwan	20-49 Years	2 doses on 28 days apart	Yet to enter Phase 3 for efficacy trial	Medigen Vaccine Biologics Corp.; Dynavax, Taiwan	(COVID19, 2021; Hsieh et al., 2021)
ZyCoV-D	DNA vaccine (plasmid)	Intradermal	Approved under WHO emergency use only in India	>18	3 doses on 28 days apart	66.6%	Zydus Cadila, India	(COVID19, 2021; Momin et al., 2021)
Spikogen/ COVAX-19	Recombinant protein subunit vaccine	intramuscular injection	Approved under WHO emergency use only in Iran	>18	2 doses on 21 days apart	-	Vaxine Pty Ltd.; CinnaGen, Iran	(Chavda et al., 2021; COVID19, 2021)
SARS-CoV-2 Vaccine (Vero Cells)	Inactivated Vaccine	intramuscular injection	Approved under WHO emergency use only in China and Indonesia	>18	2 doses on 28 days apart	-	Minhai Biotechnology Co.	(COVID19, 2021)
TAK-919	RNA	intramuscular injection	Approved under WHO emergency use only in Japan	>20	2 doses on 28 days apart	-	Moderna formulation	(COVID19, 2021)
COVI-19 inactivated vaccine/ COVIran/ Barekat	Inactivated vaccine	intramuscular injection	Approved under WHO emergency use only in Iran		2 doses on 28 days apart	-	Shifa Pharmed Industrial Co.	(COVID19, 2021)
Covovax	Protein subunit vaccine	intramuscular injection	Approved under WHO emergency use only in IIndonesia and Philippines		2 doses on 21 days apart	80-90%	Novavax formulation and Serum Institute of India)	(COVID19, 2021; Heath et al., 2021; Novavax, 2021)

concentrations of serum lipase and/or amylase (Banks et al., 2013). Consequently, it is critical to control and monitor the blood sugar level in infected diabetic patients for the management of COVID-19.

4.10. COVID-19 and unusual manifestations

The unusual and atypical manifestations of COVID-19 included rheumatologic skin disease, pulmonary and immune thrombocytopenia, large-vessel stroke, subacute thyroiditis, pedo, oral lesion, and angiogenesis associated ARDS. Also, the cross-reactivity between SARS-CoV-2 antigens and antibodies has been observed in individuals with systemic lupus erythematosus, systemic sclerosis, and rheumatoid arthritis (Arora et al., 2020). As a result, COVID-19 individuals may experience viral arthritis and musculoskeletal discomfort. Moreover, several other unusual manifestations were reported in COVID-19 patients; for instance, COVID toes (lesions) (Beuscher and Andrews, 2020), COVID tongue (Pang et al., 2020), COVID long (symptoms may last for weeks or even months after recovery of the virus), Kawasaki disease (Rehman et al., 2020), loss of taste or smell (Printza et al., 2021), severe appetite loss (Di Filippo et al., 2021), headaches (Seth and Kushwaha, 2020), dizziness and confusion (Saniasiaya and Kulasegarah, 2020), hallucinations (Clouden, 2020), blood clots (Biswas et al., 2021), hearing loss (Beckers et al., 2021), and high blood sugar (Hu et al., 2020).

5. Microbial co-infections in COVID-19

Microbial coinfection has been noticed to play a critical role in SARS-CoV-2 infection development by complicating diagnosis, treatment, and prognosis of COVID-19, and by raising illness symptoms and death rates (Koehler et al., 2020). Thus, clinical data from SARS-CoV-2 co-infection can be particularly helpful in directing the evidence-based COVID-19 therapy. A recent study suggested that patients with severe SARS-CoV-2

Table 3
List of COVID-19 vaccines under clinical trials.

Phase	Vaccines in clinical trials (Craven, 2021)
Pre-clinical	AAVCOVID, ChAd-SARS-CoV-2-S, HaloVax, LineaDNA, and PittCoVacc.
Phase 1	IN-B009, 202-CoV, CoVepiT, ReCOV, SC-Ad6-1, Noora, NBP2001, SpFN, KBP-201, MV-014-212, COVI-VAC, CORVax12, MVA-SARS-2-S, pVAC, AdimrSC-2f, bacTRL-Spike, DelNS1-2019-nCoV-RBD-OPT1, UQ-CSL, V451, and COVAC-2.
Phase 2	COH04S1, Covigenix VAX-001, PTX-COVID19-B, and VXA-CoV2-1.
Phase 1/2	AdCLD-CoV19, Soberana 1, QazCoVac-P, DelNS1-nCoV-RBD LAIV, GLS-5310, IVX-411, KD-414, VBI-2902a, VBI-2905a, and VBI-2901, COVID-eVax, S-268019, EXG-5003, AKS-452, DS-5670a, ABNCoV2, EuCorVac-19, Mambisa (CIGB 669), IIBR-100, AG0301-COVID19, ARCT-021 (LUNAR-COV19), and AV-COVID-19.
Phase 3	TURKOVAC (ERUCOV-VAC), ARCoV, VLA2001, Corbevax, Vidprevtyn, Nanocovax, V-01, Razi Cov Pars, and GBP510.
Phase 1/2/3	BNT162.
Phase2/3	Bacillus Calmette-Guerin (BCG) vaccine, CVnCoV, INO-4800, UB-612, GRAd-COV2, SCB-2019, BBV154, GX-19N, HDT-301, and (HGCO19).

infections were at a far higher risk of co-infection with other microbial infections, including viruses, bacteria, and fungi, by comparison to individuals enduring moderate infection (Koehler et al., 2020). For instance, invasive pulmonary aspergillosis was detected in 9 out of 27 (33%) COVID-19 patients under intensive care unit (ICU) (Alanio et al., 2020) while 5 out of 19 admitted patients were found with co-infections, revealed after autopsy histopathology (Koehler et al., 2020). According to Zhou et al., subsequent bacterial infections killed 50% of COVID-19 patients (Zhou et al., 2020b). In some cases, patients with prior chronic bacterial infections developed the chronic obstructive pulmonary disease (COPD) after infection by SARS-CoV-2 (Zhou et al., 2020b). Moreover, it has also been reported that co-infection with SARS-CoV-2 and HIV (human immunodeficiency virus) may impair the immune system, abnormal polyclonal activation, damage T-cells, and may further contribute to the prolongation of COVID-19 (Wang et al., 2020d).

6. Clinical approaches for COVID-19 management

The unpredictable and heterogenous symptoms ranging from mild and moderate up to severe manifestations have been identified as the most devastating feature of COVID-19, as summarized in Box 1. In fact, different types of symptoms and complications have been reported during COVID-19; therefore, to provide the best supportive care, proper management of infected individuals has been recommended based on their clinical manifestations. For example, acute COVID-19 patients were identified for a sudden drop in the oxygen level co-linked with other clinical deteriorations, such as rapid progressive respiratory failure, severe pneumonia, sepsis, ARDS, and multi-organ dysfunctions; detailed in Box 1. Consistent with it, a set of infected population displayed only mild to moderate symptoms such as headache, fever, cough, sore throat, fatigue, malaise, muscle pain, vomiting, nasal congestion, and diarrhea (Chen et al., 2020a; Guan et al., 2020a; Huang et al., 2020). Therefore, the mode of medical treatment in COVID-19 patients has been recommended based on the signs and symptoms of infection. For example, patients with a mild infection, who do not need hospitalization, are recommended to undergo self-isolation protocols to contain the virus infection. Meanwhile, patients with severe SARS-CoV-2 infection are advised for airway management and oxygen therapy along with continuous monitoring for the complications such as AKI, acute liver injury, and acute cardiac injury; ideal ventilator support has been highly recommended in case of ARDS. The chances of co-infection also persist under COVID-19; therefore, based on the initial observations and ongoing viral/bacterial disease, the administration of suitable antimicrobials drugs has been advised within an hour of sepsis diagnosis (Chen et al., 2020b; Russell et al., 2021). Along with the management and

Table 4
List of COVID-19 drugs in Phase 3 and Phase 4 of clinical trials.

Drugs	Status	Developed by	References
Remdesivir	FDA approved	Gilead Sciences	(Goldman et al., 2020; Jacobson et al., 2021)
Ivermectin	Phase 3	NeuTech Pharma	(Caly et al., 2020; Caricchio et al., 2021)
Octagam	Phase 4	OctaPharma	–
Favipiravir	Phase 3	Promomed, LLC	–
Hydroxychloroquine	Phase 3	UNICEF	(Bhimraj et al., 2020; Chen et al., 2020c; Gao et al., 2020; Gautret et al., 2020)
Tocilizumab	Phase 3	Hoffmann-La Roche	(Rosas et al., 2021)
CD24Fc	Phase 3	OncoImmune, Inc.	(Tian et al., 2020)
Ivermectin and Doxycyclin	Phase 3	Dhaka medical college	(Mahmud et al., 2021)
Azithromycin/ Ivermectin/ Ribaroxaban/ Paracetamol	Phase 3	Gilberto Cruz Arteaga	(Arshad et al., 2020; Choudhary and Sharma, 2020; Gautret et al., 2020)
Ruxolitinib	Phase 3	Novartis Pharmaceuticals	(Caricchio et al., 2021; Sedhai et al., 2021)
Canakinumab	Phase 3	Novartis Pharmaceuticals	(Caricchio et al., 2021; Sedhai et al., 2021)
Enoxaparin and Prophylactic/ Intermediate Dose Enoxaparin	Phase 3	Northwell Health	–
Proxalutamide	Phase 3	Applied Biology, Inc.	(Goren et al., 2020; McCoy et al., 2021a; McCoy et al., 2021b; Montopoli et al., 2020)
Dornase Alfa Inhalation Solution	Phase 3	University of Missouri-Columbia	(Barnes et al., 2020; Zhang et al., 2020e; Zuo et al., 2020)
Interferon beta-1a and Remdesivir	Phase 3	National Institute of Allergy and Infectious Diseases (NIAID)	(Azzi et al., 2021; Kalil et al., 2021a; Kalil et al., 2021b; Kreuzberger et al., 2021)
Hydroxychloroquine and HCQ+AZT	Phase 3	Novartis Pharmaceuticals	
Sarilumab	Phase 2	Regeneron Pharmaceuticals	(Boyapati et al., 2021)
Remdesivir and Baricitinib	Phase 3	National Institute of Allergy and Infectious Diseases (NIAID)	(Azzi et al., 2021; Kalil et al., 2021b; Kreuzberger et al., 2021)
Tocilizumab	Phase 3	Genentech, Inc.	(Stone et al., 2020)
Hydroxychloroquine	Phase 3	National Heart, Lung, and Blood Institute (NHLBI)	(Casey et al., 2020; Self et al., 2020)
Ivermectin tablets	Phase 3	Zagazig University	–
Losartan	Phase 4	Sharp HealthCare	(Geriak et al., 2021)
Hydroxychloroquine	Phase 3	University of Minnesota	(Lofgren et al., 2020; Rajasingham et al., 2021)
Sarilumab SAR153191	Phase 3	Regeneron Pharmaceuticals	(Lescure et al., 2021)
Hydroxychloroquine	Phase 3	McGill University Health Centre/ Research Institute of the McGill University	(Boulware et al., 2020; Lofgren et al., 2020; Nicol et al., 2021;

(continued on next page)

Table 4 (*continued*)

Drugs	Status	Developed by	References
		Health Centre University of Manitoba University of Alberta	Skipper and Boulware, 2021; Skipper et al., 2020)

treatment of symptomatic patients, the early recognition and screening of asymptomatic patients have been critically suggested for the interruption of SARS-CoV-2 transmission.

The clinical approaches for the management of infected patients can varied according to the COVID-19 manifestations (Varghese et al., 2020). For example, among the various recommended clinical approaches in the treatment of COVID-19 patients, only a few of them were found effective, including oxygen therapy along with ventilator via various measures in case of respiratory failure and hypoxic conditions, use of anti-viral drugs to minimize the progression of SARS-CoV-2 infection as well as to prevent other microbial co-infections, use of dexamethasone and hydroxychloroquine drugs for diabetic COVID-19 patients, and convalescent plasma therapy (CPT). In individuals with respiratory failure and hypoxic conditions, oxygen therapy was also suggested through high flow nasal cannula (HFNC), non-invasive ventilation (NIV), and invasive mechanical ventilation (IMV) (Attaway et al., 2021). In addition, different types of vaccines are already approved by World Health Organization (WHO) under emergency and other therapeutics are being tested under clinical trials (Tables 2-3). Besides, antiviral drugs are considered as the best adjunctive medication while several drugs were reported with promising antiviral activity during COVID-19 management, including hydroxychloroquine, remdesivir, favipiravir, lopinavir, interleukin (IL)-6 inhibitors, corticosteroids, ribavirin, umifenovir (arbidol), tocilizumab, anakinra, and sarilumab (McFee, 2020; Varghese et al., 2020). For example, around 2000 drugs are under clinical trial; we have listed only drugs in Phase 3 and Phase 4, as given in Table 4. Consistent with it, new antiviral oral pills named molnupiravir and paxlovid were claimed effective in COVID-19 management by reducing the number of deaths as well as hospitalizations in clinical trials (Harrison, 2021; Ledford, 2021). Also, the combination of drugs, such as dexamethasone and hydroxychloroquine, have shown promising effects in the treatment of COVID-19 patients with pre-diabetic comorbidities (Lim et al., 2021; Liu et al., 2020; Tomazini et al., 2020). Moreover, several other factors, including obesity, hypertension, type 2 diabetes, metabolic syndrome, high cytokine level, high androgen level, and low vitamin D level, were suggested to promote the SARS-CoV-2 pathogenesis (Kyrou et al., 2020); therefore, a proper diet, vitamins, and immune boosters supplements, exercise, proper medication, and regular health check-ups for pre-existing comorbidities may assist to reduce the risk of SARS-CoV-2 infection.

7. Conclusion and remarks

SARS-CoV-2 virus damages almost every organ within the body; and therefore, multiple symptoms are being associated with COVID-19 currently. To avoid the worst situation becoming and complicated, every case must be evaluated promptly and with high suspicion. SARS-CoV-2 and its emerging mutants have a high potential not only to infiltrate the lungs but also holds the potential to damage other organs due to the substantial expression and distribution of ACE2 receptors in various vital organs and tissues of the human body. Additionally, rapidly growing literature also suggested the S-protein of SARS-CoV-2 contained a furin cleavage site, indicating that S-protein is highly susceptible for the activation beyond TMPRSS2 by a broad range of host proteases (Bugge et al., 2009; Coutard et al., 2020; Walls et al., 2020). Besides, activation of IFN signalling induced by S-protein was also noted to support the elevated expression of ACE2 receptor, which may facilitate viral entry (Zhou et al., 2021). Therefore, the cause of multiple organ damage in individuals affected with COVID-19 is suggested due to the involvement of multiple factors: direct viral role, inflammation, and immune responses against viral invasion, unbalanced in RAS and ACE2/angiotensin-(1–7)/MAS axis, and downregulation of ACE2 expression. Therefore, the pathogenesis of SARS-CoV-2 is characterized as a highly complicated multifactorial disease, and damaged organs should be monitored, and problems should be managed as soon as possible. Importantly, based on available literature, it can be estimated that the individuals with compromised/weak immune system or any other enduring organs/sites enriched with $ACE2^{+}$ cells in the host can be considered as a potential spot for the onset of SARS-CoV-2 before distribution to other susceptible organs via circulatory system. Moreover, physicians who are not part of COVID-19 care and treatment should be vigilant about the alternative routes of viral transmission and adopt the protocols and guidelines regarding the COVID-19 management until the situation is clear. To minimize complications and maintain adequate management of any organ condition, multidisciplinary care is essential.

Declaration of Competing Interest

Authors declares no conflict of interest.

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