Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Review

Angiotensin-converting enzyme 2 (ACE2): COVID 19 gate way to multiple organ failure syndromes

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ABSTRACT

Background: Globally, the current medical emergency for novel coronavirus 2019 (COVID-19) leads to respiratory distress syndrome and death.
Purpose: This review highlighted the effect of COVID-19 on systemic multiple organ failure syndromes. This review is intended to fill a gap in information about human physiological response to COVID-19 infections. This review may shed some light on other potential mechanisms and approaches in COVID -19 infections towards systemic multiorgan failure syndromes.
Finding: SARS-CoV-2 intervened mainly in the lung with progression to pneumonia and acute respiratory distress syndrome (ARDS) via the angiotensin-converting enzyme 2(ACE2) receptor. Depending on the viral load, infection spread through the ACE2 receptor further to various organs such as heart, liver, kidney, brain, endothelium, GIT, immune cell, and RBC (thromboembolism). This may be aggravated by cytokine storm with the extensive release of proinflammatory cytokines from the deregulating immune system.
Conclusion: The widespread and vicious combinations of cytokines with organ crosstalk contribute to systemic hyper inflammation and ultimately lead to multiple organ dysfunction (Fig. 1). This comprehensive study comprises various manifestations of different organs in COVID-19 and may assist the clinicians and scientists pertaining to a broad approach to fight COVID 19.

1. Introduction

In 2019, a novel coronavirus outbreak in China, leading to pneumonia, was documented. The World Health Organization subsequently recognized this as COVID-19 [CO - Corona, VI - virus, D - Disease, 19-a year of the outbreak] and SARS-CoV-2 by the International Committee on Taxonomy of Viruses. SARS-CoV-2 is single-stranded RNA viruses belong to the Coronaviridae (subfamily Coronavirinae). The three epidemic diseases, such as severe acute respiratory syndrome (SARS), Middle East respiratory syndrome (MERS), and COVID-19 have been caused by coronaviruses over the past two decades (de Wit et al., 2016). As of World Health Organization (WHO) released statistics on 2 April 2020, several reported cases of COVID-19 have reached 500 000 globally (Organization, 2020a). Currently, COVID-19 mortality rates are about 2.4 percent globally due to multi-organ failure, especially in geriatric populations and people with a history of other complications such as diabetes, hypertension, and cardiovascular disease (Prompetchara et al., 2020).

The main target organ for SARS-CoV-2is believed to be the lungs; however, it affects patients with evidence of multi-organ dysfunction

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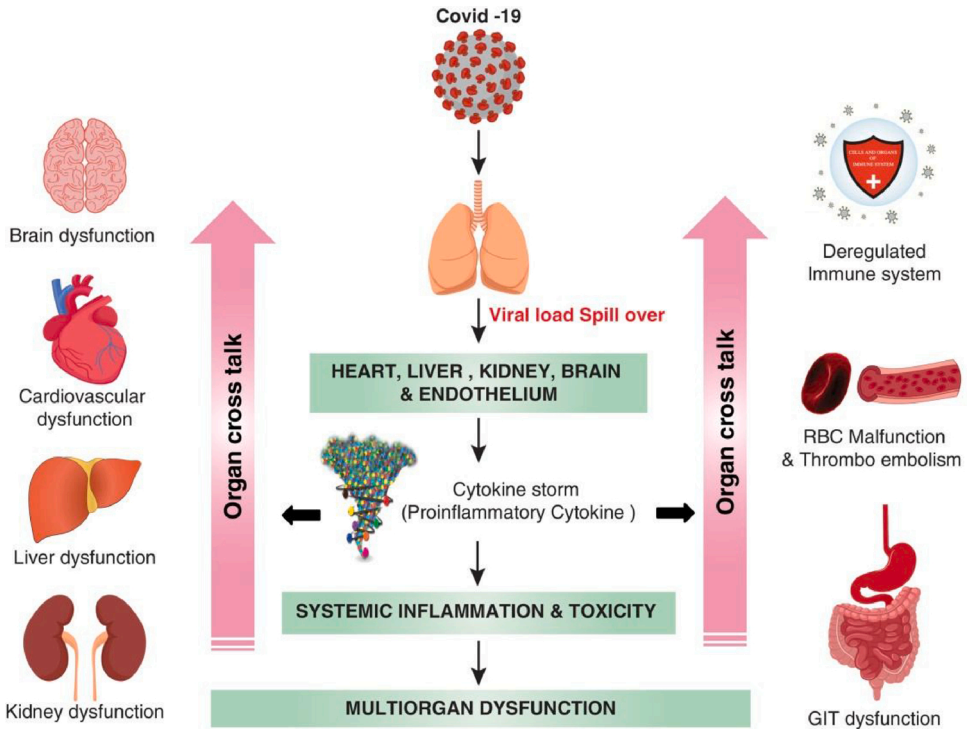

Fig. 1. SARS-CoV-2 interferes primarily with ACE2 receptors on the lungs, followed by cytokine storms with widespread release of proinflammatory cytokines, resulting in systemic inflammation with multi-organ damage to the organ crosstalk.

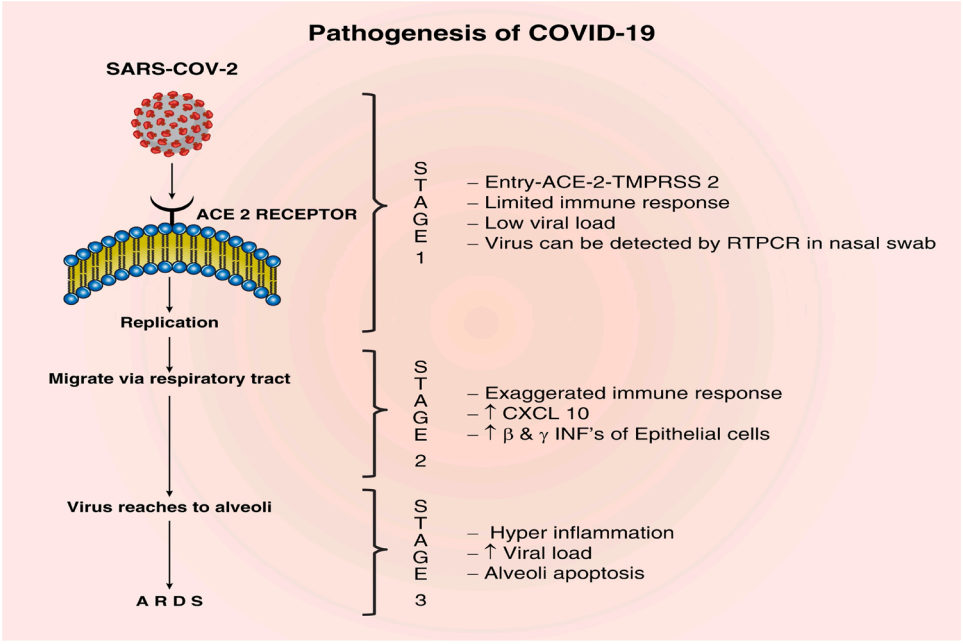

Fig. 2. In stage I, SARS-CoV-2 primarily invades type 2 pneumocytes with ACE-2 receptors (epithelial cells of the respiratory system) and under it replicates with the help of TMPRSS2. In stage II, the replicated SARS-CoV-2 virus reaches the respiratory tracts and exaggerates immune response by elevated levels inflammatory chemokine (CXCL10), β & γ INF's of epithelial cell. Further rise in SARS-CoV-2 viral load in stage III contributes to hyperinflammation, alveolar apoptosis and ultimately leads to acute respiratory distress syndrome (ARDS).

such as heart, liver, kidney, stomach, intestine, blood and immune system (Wang et al., 2020c; Wong et al., 2020). Already the world is witnessing the COVID-19 deleterious impressions on life and health. The world is now experiencing the harmful effects of COVID-19 on life and wellbeing. However, the symptoms, clinical manifestations, receptor-mediated mode of action, and in vivo transmission contribute to multi-organ failure has not yet been fully understood so far. Hopefully, this review will provide the current and updated literature about the SARS-CoV-2 manifestations in particular focus to various organs (i.e. extrapulmonary manifestations).

1.1. Routes of transmission

Structural analysis reveals the atomic level-specific communications between spike protein receptor-binding domain of SARS-CoV2 and ACE2 receptor present in the host to regulates the transmission of cross-species and human to human (Fig. 2). SARS-CoV-2also uses ACE2 as its binding receptor, to transfer from human to human. The transmission of the SARS-CoV-2virus is possible from asymptomatic, presymptomatic, symptomatic, and COVID-19-infected persons (Organization, 2020b). The virus transmission from the asymptomatic person that does not

show symptoms is notable and needs attention. Alternatively, information from a presymptomatic individual can also occur before the onset of symptoms (i.e., during the time of incubation). Droplets (coughing or sneezing) and close contact play a central role in COVID-19 infection and human to human transmission. The probable asymptomatic incubation period of COVID-19 is varied from 2 to 14 days, and the mean incubation period is around five days (Lauer et al., 2020). Hence, the symptoms may manifest in the individual from 2 days to 2 weeks after viral exposure. The SARS-CoV-2 virus has spike protein receptor binding and may use ACE2 as a functional receptor in stage 1 (Fig. 2) for cellular entry ACE2 (Hoffmann et al., 2020) and leads to COVID-19 pathogenesis.

The SARS-CoV-2 genome consists of nucleotides nearly more than 30,000 and encodes four structural proteins includes, Membrane protein, Spike protein, Envelope protein and nucleocapsid protein with several non-structural proteins. The capsid contains N-protein or nuclear capsid that binds to the single positive strand viral RNA that permits the virus to take over the human cells and convert them into viral factories. Additionally the N protein that coats the viral RNA genome plays a major role in transcription and replication. The spike protein on SARS-CoV-2 binds with ACE2 receptors on the surface of various cells mainly via the lungs causing the viral entry, where E protein's ion channel activity is found on the transmembrane region of the protein. E protein found to have a vital role in regulation and control of ion influx and efflux and thus the intracellular and extracellular environment. Hence, the ion conductivity triggered by E-protein via the manipulation of SARS-CoV-2genome may seem to be a novel route involved in pathogenesis of virus.

1.2. Receptor mediated mechanism of action

Ironically, ACE2, a gene mainly found in vascular endothelium in all structures such as type I and type II pneumocytes, smooth muscle cells in the pulmonary vasculature, bronchial epithelium, epithelial cells in the lungs, heart, intestine, blood vessels, testes and kidneys (Hamming et al., 2004; Imai et al., 2020). SARS-CoV-2 (S protein) and ACE2 complex cleave S1 from S2 directly binds to the ACE2 RNA binding domain (RBD) (Fig. 3). The ACE2 extracellular peptidase domain recognizes RBD via polar residues and facilitates viral entry through the direct plasma membrane and viral membrane fusion (Belouzard et al., 2009). Once entered into the host cells, Viral RNA genome translation occurs in the cytoplasm to form two structural proteins and polyproteins, that further assists the virus progeny assembly and eventually forms enveloped glycoproteins and genomic RNA within the protein machinery (Li et al., 2020a,b;c; Perlman and Netland, 2009). In the cytoplasm, structured protein nucleocapsids were combined with accessory proteins, genomic RNA, and R protein in the endoplasmic reticulum, eventually release the virions through exocytosis from the infected cell (Shereen et al., 2020). The released infected viral particle readily binds with ACE2 receptors elsewhere (Wu and McGoogan, 2020) and the process continues.

1.3. COVID-19 with oxidative burst systemic inflammation

In response to viral and bacterial infections, the immune system develops both proinflammatory and anti-inflammatory cytokines. Following exposure to antigen-presenting cells (APCs) by SARS-CoV-2antigen, T cells release cytokines in various T cell subsets. They may further amplify the release of cytokine (cytokine storm) (Fig. 4) implies positive feedback between immune cells and cytokines (Kouhpayeh et al., 2020). Alternatively, the genomic dsRNA virus may activate interferon regulatory factors and the NF-κB pathway, which releases enormous type I interferons and proinflammatory cytokines (Li et al., 2020c,d). The increased serum IL-6, C-reactive protein, and TNFα (Zhou et al., 2020a,b). TNFα (Huang et al., 2020) are likely to involve the proinflammatory condition in COVID-19 disease. The disease severity indicates the alteration in proinflammatory cytokines such as IL-7, IL-, IL-10, G-CSF, TNFα, IP-10, MIP-1A, MCP-1, in patients with COVID-19 (Huang et al., 2020). Proinflammatory cytokines have been shown to encourage reactive oxygen species and the formation of free radicals that lead to oxidative stress and, ultimately, apoptosis and necrosis due to NAD + and ATP exhaustion (Kouhpayeh et al., 2020). Like neutrophils and macrophages, the activated phagocytes create vast quantities of reactive oxygen species and reactive nitrogen species to kill the invading agents during the inflammatory process. These intracellular sources of free radical generation may be subject to oxidative stress-induced DNA damage during viral infection (Kryston et al., 2011). In COVID-19 patients, oxidative stress and proinflammatory cytokines cause tissue damage mediated by inflammation. Therefore, oxidative stress and immune response deregulation result in cytokine storm, and pro-inflammation could lead to various organ dysfunctions in SARS-CoV-2 infection (Chen et al., 2020a) (Table 2).

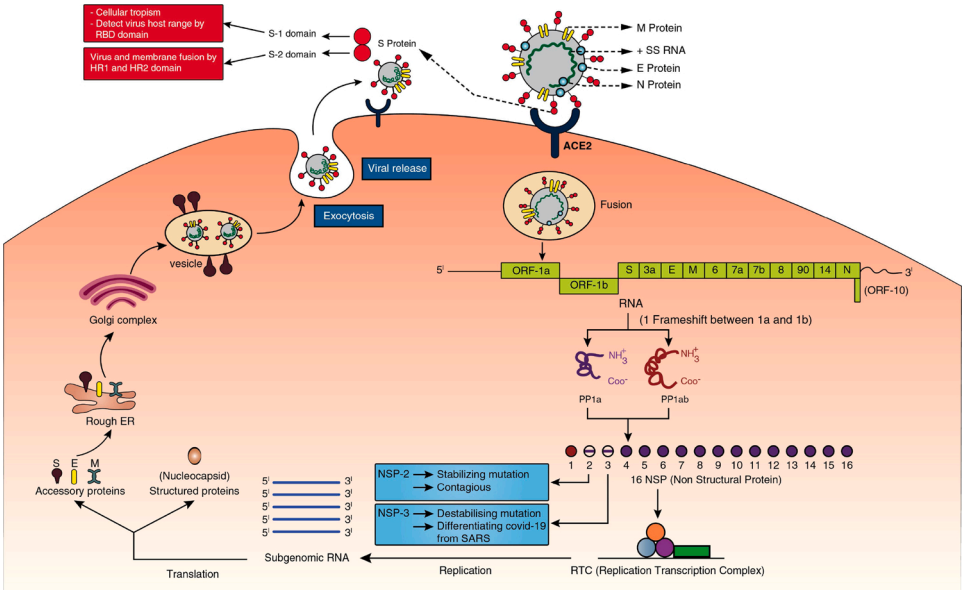

Fig. 3. SARS-CoV-2 life cycle which starts with the binding of S-protein to the ACE2 receptor. Conformational changes in S-protein after binding support the fusion of viral membrane with the cell membrane (the endocytosis mediated by Receptor). It triggers the release of RNA into the cytoplasm by SARS-CoV-2. The frame shift (-1) between 1a and 1b of RNA results in the creation of two polyproteins (pp1a and pp1ab) encoding non-structural proteins and forming transcription complex replication, in turn undergoing replication and synthesising the subgenomic RNA. Subsequently it is converted into accessory proteins (S, E, M) and structural proteins (Nucleocapsid). The newly developed genomic RNA, nucleocapsid, and enveloped glycoproteins assembled via endoplasmic reticulum and golgi complex to form viral particle buds. Finally, the vesicle that contains the virion fuses with the plasma membrane, resulting in viral release through exocytosis.

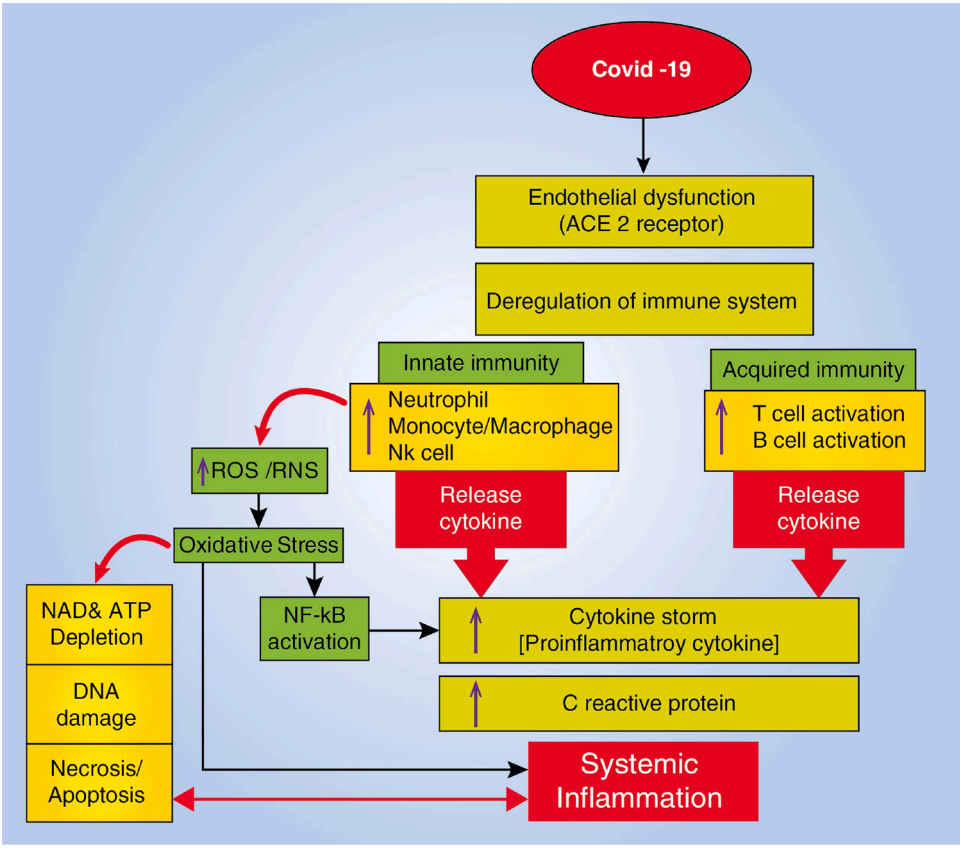

Fig. 4. SARS-CoV-2 attacking the endothelial cell and deregulating the immune system, leading to cytokine storm, oxidative stress and pro-inflammation contributing to systemic inflammation and toxicity with multi-organ dysfunction.

1.4. COVID-19 and immune cells

The immune system is the multi-stage network for protecting the body against harmful bacteria, viruses, and other organisms. COVID-19′s occurrence and development are mediated by viruses and the individual's immune system (Abdulamir and Hafidh, 2020). The human self-immune system is the earliest tool to combat COVID-19. There has been little work on the relationship between SARS-CoV-2 and damage to immune cells (Table 1). This review curiously focused on understanding the interaction between the host immune system and the COVID-19 outbreak based on accumulated data. The genetics of the immune system, e.g., HLA genes, can determine the individual infection, duration, severity, relapse, and reinfection (Li et al., 2020a,[Li et al., 2020b] b). Also, the age factor is positively correlated with the SARS-CoV-2 viral load and clarifies the disease's severity in older patients (Huang et al., 2020; Xu et al., 2020a,b,c,d,e,f,). The aged population is prone, which could be the low immunity with higher viral load (Y. Chen and Li, 2020). Ironically, by resting at home (self-quarantine), the infected individuals or patients can cure themselves with acute COVID-19 infection (Cascella et al., 2020). It helps our immune cells to combat disease with COVID-19 and prevents transmission. The self-immune cells serve as a barrier, delay the virus's replication, and produce defensive antibodies and avoid further infections. In response to infection, the proliferation of T-cells may take a week to boost their condition. However, patients may rapidly worsen as the infected cell proliferates beyond the point where T-cells' efforts become helpless. Approximately 80 % of COVID-19 patients experience a transition from mild to moderate with symptoms or no symptoms at all during this week. Yet, in the current situation to understand the immune responses is essential. Endothelium, one of the first line of the body defence system, plays a part in controlling the immune system through various receptors and cytosolic proteins (Takeuchi and Akira, 2010). Endothelium secretes cytokines to regulate innate and adaptive immune responses, and at the site of action, it recruits immune cells (Marelli-Berg and Jarmin, 2004). SARS-CoV-2 targets the endothelial host cell by binding its spike glycoprotein to the ACE2 receptor (Marelli-Berg and Jarmin, 2004). SARS-CoV-2 targets the endothelial host cell by binding its spike glycoprotein to the ACE2 receptor (Lovren et al., 2008; Sardu et al., 2020), which is highly expressed in lungs (Hamming et al., 2004). Endothelial activation increases vascular permeability to plasma proteins, releases pro-inflammatory cytokines, tumour necrosis factor-1d6fc; (TNF-1d6fc;), chemokines, adhesion molecule (from activated leukocytes) and induces inflammation (Pober and Sessa, 2007). The endothelial dysfunction stimulates a sequence of signalling molecules releasing nuclear factor-kB (NF-kB) to control both the innate and adaptive immune response (Oeckinghaus and Ghosh, 2009). If an innate immunity effort fails to abolish threat, it activates adaptive immune reactions and converts the acute inflammation into chronic inflammation (Seledtsov et al., 2015).

Innate immune response: Innate immune responses to COVID-19, such as increased neutrophil, reduced lymphocyte, are related to infection and severity of disease and eventually contribute to the death of patients (Wu et al., 2020b; Zhou et al., 2020a,b). Probably the leading cause of the life-threatening respiratory situation in COVID-19 patients is due to the secretions of granulocytes, and proinflammatory macrophages that damage cells and induce innate inflammation in the lungs (Xu et al., 2020a,b,c,d,e,f,). The lower frequency of recruitment of monocytes (CD16 + CD14 +) in the COVID-19 patient's blood, shows the infection (Thevarajan et al., 2020),with no difference in frequency of NK (natural killer) cell (Thevarajan et al., 2020). Effective innate immune responses to control the viral replication against viral infection depend on the Interferon-1d6fc; (IFN-1d6fc;) and Toll-like receptors 3 (TLR3) expressions (Kawai and Akira, 2006). Endothelium chiefly expresses both

Table 1
COVID-19 and multi organ failure syndrome.

Article	Objective	Conclusion	References
COVID-19 and immune cells			
Case report	To find the pathology of a COVID -19 patient died with acute respiratory syndrome (ARDS). (by obtaining biopsy samples at autopsy)	CD4 T cells as well as CD8 T cells were activated (as indicated by high HLA-DR) although they had significantly less count. There was also a high level of proinflammatory factor in CD4 T cells, and a high level of cytotoxic granules in CD8 T cells.	(Xu et al., 2020a)
Review	A comparison of COVID -19 with SARS-CoV and MERS-CoV with a pathogenesis of host-immune interaction	As similar to SARS-CoV and MERSCoV, Th1 cell response can be fruitful in regulating COVID -19. The $CD8^{+}$ T cell response to COVID -19 infections should be monitored to prevent lung damage.	(Prompetchara et al., 2020)
Review	To control immune modification during COVID -19 pneumonia as compared to SARS and MERS	The pathological change in immune response with COVID -19 infections during pneumonia remains unknown until now and thus no known antiviral drug against this virus.	(Lin et al., 2020)
Review	To brief molecular improvement in immune pathology in COVID-19 based on infections with SARS-CoV and MERS-CoV.	The immune system influences of the person include human leukocyte antigen (HLA genes), when a person is infected with SARS-CoV-2 virus, prolongation and serious form of the disease, and reinfection.	(Li et al., 2020a)
Editorial	To Observe immunological response of COVID-19-infected patient.	Multi-factorial immune responses with high levels of antibody-secreting cells (IgM and IgG antibodies) and CD4 T cells and CD8 T cells with more activation Up to recovery in the blood.	(Thevarajan et al., 2020)
Editorial	To observe the heterogeneity of Haplotype HLA-loci in COVID-19 infection	Successful removal of COVID-19 infection is based on the infected individual's health status and HLA (major histocompatibility complex) system. Hence HLA typing can play a major role in COVID-19 treatment and prevention (preparing the vaccine).	(Shi et al., 2020)
COVID-19 and lung			
Commentary	Does DPP4 (type II transmembrane glycoprotein) inhibition: prevents COVID-19 infection and/or progression?	SARS-CoV-2 uses DPP4 has a utility receptor for cellular adhesion, hence inhibition of DPP4 may be a remedial strategy to avoid infection.	(Iacobellis, 2020)
Research article	Whether COVID-19 viral pathogenesis has been decreasing at high altitude?	High altitude decreases half-life of the virus, and hypoxia mediates down regulation of pulmonary epithelial ACE-2 (SARS-CoV-2 receptor)	(Arias-Reyes et al., 2020)
Research article	By using human recombinant soluble ACE2 to suppress infections of COVID-19 in engineered human tissue	Human recombinant soluble ACE2 (hrsACE2) blocks COVID-19 growth (by inhibiting ACE-2 interaction), but it has no impact on mouse rsACE-2, which helps prevent early COVID-19 infections.	(Monteil et al., 2020)
Research article	Possibility to use lambda interferon against viral load and SARS-CoV-2 induced hyperinflammation.	Tuning of antiviral immunity in the respiratory tract and reducing harm to the host.	(Ziegler et al., 2020)
Brief communication	Identification in nasal epithelial cells of the associated gene COVID-19 along with innate immune genes.	High expression of SARS-CoV-2 entry factors of nasal epithelial cells along with innate immune genes leads to initial infection and spread of the virus.	(Sungnak et al., 2020)
Review article	Vitamin D additive can decrease the risk of Influenza and COVID-19 Infections and Deaths	Vitamin D can decrease the chance of infections by stimulating cathelicidins and defensins, which may decrease the rate of viral replication and decrease the rates of pro-inflammatory cytokines (injuring the lung, causing pneumonia).	(Grant et al., 2020)
Case study	The role of chest CT in COVID 19 diagnosis and management	Chest CT had a low rate of missed COVID-19 diagnosis (3.9 %, 2/51) and could be a standard approach for improving COVID-19 patient care. But it doesn't differentiate between viruses.	(Li and Xia, 2020)
Case study	Differentiating the clinical and CT characteristics in pediatric patients with COVID-19 adult infection	In pediatric patients elevated procalcitonin and consolidation with surrounding halo signs were normal, but different from adults.	(Xia et al., 2020)
Case study	How Melatonin acts as a possible adjuvant for treatment with COVID-19.	Melatonin (anti-inflammatory and anti-oxidant molecule), is safe against ALI / ARDS from viral and other pathogens. Efficient in treating COVID-19 patients with improved health outcomes (by reducing vessel permeability, anxiety, use of sedation, and improving quality of sleep).	(Zhang et al., 2020a)
Editorial	Anti-inflammatory approaches against pro-inflammatory cytokines (IL-1 and IL-6) and COVID-19-caused lung inflammation. .	IL-37 and IL-38 function as potential therapeutic cytokines which inhibit pro-inflammatory cytokine release. .	(Conti et al., 2020)
Research article	Renin-angiotensin system inhibitors may be a safe alternative for COVID-19 pneumonia therapy	In COVID-19 patients with pneumonia, angiotensin-converting enzyme inhibitors and angiotensin II type 1 receptor antagonists inhibitors may reduce inflammatory response and mortality in the pulmonary system.	(Sun et al., 2020b)
Case study	Serial computed tomography finding in COVID-19 pneumonia	Progress in both lungs with peripheral consolidations and ground-glass opacities. The lesions were removed after treatment leaving the fibrous lesions behind.	(Wei et al., 2020)
Research article	The risk of severe COVID-19 increases with angiotensin-converting enzyme inhibitors and angiotensin blockers	Increases the receptors of ACE2, and acts as binding sites in the lungs for SARS-CoV-2 virions.	(Diaz, 2020)
Research article	ACE-2 Expression in Small Airway Epithelia of smokers and COPD Patients: Implications for SARS-CoV-2 Expression of ACE-2 in Small Airway Epithelia of Smokers' and COPD Patients': Implications for COVID-19	In COPD patients and smokers the expression of ACE-2 in small epithelial cells of the airway has increased. ACE -2 is the SARS-CoV-2 entry receptor that contributes to serious infections.	(Leung et al., 2020)
Research article	COVID-19 pathogenesis from a perspective of cell biology	The magnitude of COVID-19 can be understood by portion of the infected lung. Gas exchange section of the lung was involved in moderate infection, bringing airways and serious infection.	(Mason, 2020)
Research article	Could nicotine protect a person against COVID-19?	Nicotine may block entry of the virus via olfactory system or lung cells. Immune cells, neurons, lungs, cardiac tissue and blood vessels attributable to nicotine receptors (nAChRs).	(Olds and Kabbani, 2020)

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Table 1 (*continued*)

Article	Objective	Conclusion	References
COVID-19 and liver			
Comments	Assessed how the liver is affected using the available case studies in Beijing, China.	Patients with severe COVID-19 tend to be experiencing elevated levels of liver dysfunction.	(Zhang et al., 2020a)
Review	To what extent chronic liver disorders should be considered as risk factors for COVID -19 infection	Because of additional risk factors, Non-steroidal anti-inflammatory drugs should not be prescribed in patients with cirrhosis and portal hypertension	(Boettler et al., 2020)
Guest Editorial	COVID-19 and drug induced liver injury: a problem of plenty or a pettypoint	SARS-CoV-2 infection can affect normal hepatic functions and has proven to be hepatotoxic in nature.	(Boeckmans et al., 2020)
Correspondence	COVID-19 and the liver : little cause of concern	Virally mediated cytotoxic T cells and activation of dysregulated inborn immune response can result in collateral damage to the liver.	(Bangash et al., 2020)
Commentary	COVID-19 and liver disease	An overview of the hepatotoxicity effects based on the first published evidence on COVID 19 and Liver.	(Sun et al., 2020a)
Letter to editor	COVID-19 Liver and kidney injuries and their effects on drug therapy	Routine monitoring of liver and kidney functions in COVID-19 patients will aid in early diagnosis of liver and kidney disease	(Rismanbaf and Zarei, 2020)
Research article	Extracted 95 patients laboratory confirmed data with 2019 novel coronavirus pneumonia in Wuhan, China	Alanine aminotransferase (ALT) and Aspartate aminotransferase (AST) activity increased and approximately one third of patients with liver damage were found to be caused by multiple factors: immunity, inflammation and medication.	(Zhang et al., 2020a)
Research article	Investigated pathological characteristics in COVID-19 patients who died from extreme SARS (autopsy sample)	Microvascular steatosis (moderate level), mild lobular and portal activity suggests liver injury caused by either SARS-CoV-2 infection	(Xu et al., 2020a)
Research article	Unbiased assessment of cell type-specific expression of ACE2 in healthy liver tissues using single cell RNA-seq data from two separate cohorts and reported unique expression in cholangiocytes	SARS and 2019-nCoV patients with liver injury may be triggered by cholangiocyte injury / dysfunction and other potential causes may be induced by drug or systemic inflammatory response.	(Chai et al., 2020)
Review	The characteristics and mechanisms of liver injury caused by SARS-CoV, MERS-CoV as well as SARSCoV-2 infection	Direct virus mediated cytopathic effects and/or over-shooting immune-mediated inflammatory reactions, or drug-induced injury, may be the major factors for liver damage	(Xu et al., 2020a)
COVID-19 and kidney			
Review	Analysis of kidney functions in COVID-19 patients and their mortality relationship	The risk of COVID-19 from organ donation is small and donor screening should be compulsory. Overall, the occurrence of symptoms demands that donors delay a minimum of 14–28 days.	(Perico et al., 2020)
Observational	The study of kidney functions in COVID-19 patients and their mortality relationship	COVID-19 patients with current acute kidney injury are about (5.3-times) more vulnerable to higher mortality than patients with no acute kidney injury about (1.5-times).	(Li et al., 2020a)
Research article	Exploring renal function infection with SARS-CoV-2 by examining clinical data from the 116 hospitalized COVID-19 patients reported.	In COVID-19 infection, patient does not result in kidney injury.	(Wang et al., 2020a)
Letter to editor	To perform single-cell RNA sequencing (scRNA-seq) for the identification of a possible cause of acute kidney injury in COVID-19 patients	Shows direct cytopathic effects via ACE2 receptors on proximal straight tubule cells and podocytes, and can cause acute kidney injury in COVID-19 patients	(Xu et al., 2020a)
Research	26 Autopsies of COVID-19 patients with light microscopy	COVID 19 viral invasion into the nephrons represented by up regulation of ACE2 receptor with nucleoprotein antibody in the renal tubules in the infected COVID-19 patients.	(Su et al., 2020)
Commentary	Mechanisms and management of COVID-19-associated kidney injury.	Cytokine damage, organ crosstalk and systemic effects are profoundly to be accounted for kidney injury.	(Su et al., 2020)
COVID-19 and Brain			
Case report	Seeking neurological manifestations in hospitalized patients infected by COVID-19	COVID-19 patients are vulnerable to development of neurological disorders including loss of consciousness, acute cerebrovascular diseases and muscle skeletal injury	(Mao et al., 2020)
Case report	First 2019 novel coronavirus case disease with encephalitis in 2019 .	COVID-19 patients contain virus in the cerebrospinal fluid identified by genome sequencing, suggests viral encephalitis	(Cai et al., 2020)
Research article	With the help of CT and MRI, to find COVID-19 is associated with acute necrotizing hemorrhagic and encephalopathy	COVID-19 is associated with acute necrotizing haemorrhagic, encephalopathy and altered mental state.	(Polak et al., 1998)
Case report	Analysis of gustation and olfaction disorders in patients with serious acute respiratory infection with COVID-19.	Olfactory and taste disorders (OTDs) often occurred in patients diagnosed with COVID-19 and this may precede the onset of full-blown clinical illness.	(Giacomelli et al., 2020)
Research article	In COVID-19 infected patients, elucidate the underlying pathogenicity found in olfactory and taste.	Large expression of ACE2 receptors on oral mucosa epithelial cells in COVID-19 patients.	(H. Xu et al., 2020a)
Review	Post involvement of the nervous system following COVID-19 infection	COVID-19 in conjunction with the host immune system induces inflammatory cytokines and this may result in chronic infections leading to neurological complications.	(Y. Wu et al., 2020a)
Review	Neuroinvasive ability of COVID-19 in respiratory failure.	The Brain glial cells and neurons express ACE2, making them simple target for COVID-19.	(Baig et al., 2020)
COVID-19 and heart			
Review	Pathophysiology of COVID19 and its impact on cardiovascular system	Induce hype inflammation, cytokine storm, and expression of cardiac biomarkers leads to systemic toxicity.	(Akhmerov and Marban, 2020)
Comment Review	Specific attention to protect cardiovascular system during COVID-19 treatment	COVID-19 injures myocardium via ACE2 receptor.	(Ma et al., 2020)
Report	To find the relationship between COVID-19 and heart disease	Signaling alteration in COVID-19 infection can lead to heart and lung disease during treatment.	(Rizzo et al., 2020)
Review	Understanding COVID-19 patients and cardiovascular disease interaction for management	Existing understanding between cardiovascular disease and COVID-19 is insufficient and much needed for future research.	(Bansal, 2020)

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Table 1 (*continued*)

Article	Objective	Conclusion	References
Commentary	Cardiologist and treatment in COVID-19	The impact of cardiovascular drugs on COVID19 patients remain uncertain	(Ferrari et al., 2020)
Research article	COVID-19 and cardiovascular morbidity and mortality	COVID-19 patients are at elevated risk for morbidity and mortality in patients with cardiovascular comorbidity.	(Clerkin et al., 2020)
Comment	COVID-19 causes acute damage to the myocardium and chronically to the cardiovascular system	Special attention to the diagnosis and care of COVID-19 heart disease patients	(Zheng et al., 2020)
Review	COVID-19 and special emphasis on the cardiovascular system	COVID-19 induces myocarditis, arrhtymias and extremely likned to hyperinflammation	(Madjid et al., 2020)
Summary	Pandemic COVID-19 cardiovascular risk in individuals who are infected & not infected.	COVID-19 effects to extremely high-risk cardiovascular patients and society.	(Gori et al., 2020)
COVID-19 and GIT			
Commentary	To detect positive patients with GI manifestations and faecal – oral transmission in COVID-19.	The emphasis would be on the initial manifestations of COVID-19 digestive symptoms that would assist in early identification, diagnosis, early isolation, and rapid response.	(Gu et al., 2020)
Research article	To examine the prevalence and outcomes of Gastrointestinal symptoms in patients with cancer who are COVID-19 positive.	Digestive symptoms such as diarrhoea are usually seen in COVID-19 cancer patients and early increase in suspicion index should be considered in at-risk patients.	(Liang et al., 2020)
Review	To evaluate clinical features; rate of discharge; gastrointestinal COVID-19 infection	Clinicians should consider digestive symptoms, such as diarrhoea, in COVID-19 patients at risk sooner, rather than waiting for respiratory symptoms to occur. In addition, even after viral clearance from the respiratory tract, viral gastrointestinal infection and possible fecal-oral transmission will last	(Cipriano et al., 2020)
Research article	Investigating the potential route for COVID-19 transmission.	A patient who showed negative oral swabs could still shed the virus orally-fecally. SARS-CoV-2 may be transmitted through multiple routes. Both molecular and serological tests should be performed to establish the definitive carrier of the virus	(W. Zhang et al., 2020a)
Brief communication	To find evidence of recurrent faecal virus shedding in COVID-19 infection	Confirmation of cases of COVID-19 infection by oral – faecal route in 10 COVID-19 patients	(Y. Xu et al., 2020a)
Research Letter	Evidence of an asymptomatic infant who was COVID-19 positive in a stool test 17 days after the last exposure to the virus.	The child was found to be virus positive in stool specimens despite negative respiratory tract specimens for an additional 9 days	(A. Tang et al., 2020a)
Research article	The report tested the viral RNA in faeces from 71 COVID-19 patients during their hospitalisation	Analysis recommends that rRT-PCR testing for COVID-19 faecal infection should be performed regularly in COVID-19 patients	(F. Xiao et al., 2020a)
COVID-19 and RBC accompanied with thromboembolism			
Correspondence	To study the acquired acute porphyria in critical covid-19 patients	COVID-19 can alter porphyrin metabolism, decrease haemoglobin levels, increased total bilirubin levels and elevated serum ferritin levels make a chance of developing acute porphyria.	(Abrahams, 2020)
Research paper	To find risk factor in patient with COVID-19	Sepsis, increased coagulation and elevated d-dimer were a common complication in older patients with COVID-19 infection.	(F. Zhou et al., 2020a)
Research paper	Epidemiological and clinical characteristics of 2019 novel coronavirus pneumonia.	In several patients the amount of lymphocytes and haemoglobin was below normal levels. However, increased C-reactive protein, alanine aminotransferase or aspartate aminotransferase is caused by viral infection due to drug hepatoxicity or liver dysregulation.	(Menk et al., 2018)
Research paper	To study the clinical features of cancer patients contaminated with COVID-19.	Patients with cancer had a clinical profile similar to other non-cancer cases, except for anaemia and hypoproteinemia.	(N. Chen et al., 2020a)
Letter to editor	Laboratory abnormalities in patients with COVID-2019 infection	Laboratory abnormalities in patients with COVID-2019 infection Decreased haemoglobin and neutrophil counts and increased serum ferritin, total bilirubin, sedimentation rate of erythrocytes, C-reactive protein, albumin, and LDH. This result suggests erythrocyte involvement in the pathophysiology of Covid-19.	(L. Zhang et al., 2020a)
Research paper	A Tool to early predict severe 2019-Novel Coronavirus Pneumonia (COVID-19)	Index such as Older Age, Higher LDH, CRP, Red Blood Cell Distribution Width (RDW), Direct Bilirubin, Blood urea nitrogen and Lower Albumin, validated the prognostic nomogram to determine disease severity.	(Lippi and Plebani, 2020)
		Among these, RDW was a strong prognostic predictor for extreme COVID-19, which suggested that turnover of RBC, could result in poor COVID-19 outcome.	
Research paper	An observational research in patients with acute respiratory distress syndrome (ARDS) to see nucleated red blood cells as predictors of mortality.	Nucleated red blood cells (NRBCs) are normally absent in healthy adult peripheral blood which cause elevated rates of pro-inflammatory cytokines, arterial hypoxemia and compensatory erythropoiesis. A total of 404 patients with essential ARDS were examined in which 75.5 % of the patient shows NRBCs in the blood.	(Gong et al., 2020)
Research paper	Relationship between Red Cell Distribution Width (RDW) and Mortality in Critically unwell patients with Acute Respiratory Distress Syndrome	Inflammatory reactions and inflammatory cytokines may affect bone marrow function, repressed erythrocyte growth, resulting in high reticulocytes, and increased RDW. As such, RDW can be used as an effective prognostic marker in critically ill patients with ARDS	(Wang et al., 2019)
Research paper	Investigating the interaction between the blood group ABO and vulnerability to COVID-19.	Blood group A has a higher risk of infection with COVID-19, while Blood group O could be at lower risk due to the existence of anti-A antibodies that inhibit the attachment of SARS-CoV-2 protein-expressing cells to ACE2 (SARS-CoV-2 spike protein cell receptor).	(Guillon et al., 2008; Zhao et al., 2020)
Research paper	To find blood clotting disorder in COVID-19 infected patients	Hemostasis was deranged with a significant depletion of coagulation factors contributing to the risk of developing intravascular disseminated coagulation (DIC).	(Han et al., 2020)
Research paper	To find association of abnormal coagulation with COVID-19 pneumonia	Abnormal coagulation with COVID-19 pneumonia was significantly elevated	(N. Tang et al., 2020a)
Editorial	Relating acute aortic thrombosis to pulmonary embolism makes COVID-19 pneumonia difficult	Hypercoagulable condition followed the patient with acute abdominal aorta thrombosis, as well as pulmonary embolism.	(Le Berre et al., 2020)

IFN-1d6fc; and TLR3 (Tissari et al., 2005) and TLR9 against virus and bacteria (El Kebir et al., 2009). Hence, highly efficient innate immune responses in young children could be a reasonable explanations for less severe SARS-CoV-2 infection (Kelvin and Halperin, 2020). These facts indicate strongly that the innate immune response may act as a vital factor for the outcome of a disease.

Acquired immune response: CD4 + T cells and CD8 + T cells play a significant role in developing autoimmunity or anti-inflammation (Cecere et al., 2012). CD4 + T cells specifically stimulate the production of virus-specific antibodies and the activation of T-dependent B cells (Xiaofeng Li et al., 2006). CD8 + T cells are directly cytotoxic to the virally infected cells (Doherty et al., 1997). However, the expression and survival of CD4 + T cells and CD8 + memory T cells depend on endothelium (Shiao et al., 2005). Among SARS-CoV-2 -infected patients, the number of CD4 + T cells and CD8 + T cells in the blood has been substantially decreased, showing evidence of excessive activation with elevated levels of HLA-DR (Xu et al., 2020a,b,c,d,e,f,). Moreover, increased concentration of proinflammatory substances in CD4 + T cells and cytotoxic granules in CD8 + T cells account for severe immune insults in this patient (Xu et al., 2020a,b,c,d,e,f,).

Multi-factorial immune responses such as increased antibody-secreting cells, helper T cells, activated CD4 + T and CD8 + T cells, IgM, and IgG antibodies were detected non-severe COVID-19 recovered patient's blood (Thevarajan et al., 2020). Contrary to this, IgM & IgG antibodies were simultaneously increased on day 10th following the onset of symptoms in 23 patients with COVID-19 (To et al., 2020) and this may clarify the neutralising activity of the antibodies with the surface spike receptor-binding domain of SARS-CoV-2 virus (Y. Chen and Li, 2020). The vulnerable SARS-CoV-2 nduces hardly any chronic symptoms after incubation and provokes protective immune responses. During the incubation period, the body develops multiple approaches to improve immune responses. The successful eradication of the SARS-CoV-2 consequences relies on the infected individual health status and antigen loci of major-histocompatibility complex (HLA) (Li et al., 2020b). In case the infected personal general health and HLA haplotype (which elicits specific antiviral immunity) are unable to cope with the viral infections he/she may enter a severe stage and encounter the intense detrimental inflammatory response, especially in the lung (Li et al., 2020b). Henceforth more detailed understanding of both the innate and adaptive immune responses to SARS-CoV-2 is now essential to understanding its pathogenesis.

1.5. COVID-19 and lung

Like the SARS coronavirus, COVID-19 patients usually develop upper respiratory tract illness (Wang et al., 2020c) (Table 1). The ACE2 receptors markedly expressed in epithelial cells of the nasal cavity, type2 alveolar cells of lungs (Abassi et al., 2020), as well as heart, liver, kidney and gastrointestinal tract. In which lungs with the larger surface are more susceptible to COVID -19. Viral S protein on SARS-CoV-2 additionally requires various cofactors, especially TMPRSS2, found to be located in alveolar pneumocytes and responsible for SARS-CoV-2 entry and infection during interaction with host cell surfaces (Lukassen et al., 2020). Notably, two proteases ADAM17 and TMPRSS2 decide the fate of ACE 2 influence on organs along with the SARS-CoV-2 towards multi-organ failure and viral pathogenesis (Heurich et al., 2014; Xiao et al., 2020a,b). The ventilatory ratio, a bedside index of lung dead space, and ventilation efficiency, is found to be increased in COVID-19 patients (Liu et al., 2020b). The major consequences and reason for life threatening are respiratory disorders at severe stages is also due to the hyper-inflammation associated with the increase in proinflammatory cytokines and depressed innate immunity (Xu et al., 2020a,b,c,d,e,f,).

Patients with chronic obstructive pulmonary disease (COPD) are known to have increased expression of ACE2 receptors leads to severe lung diseases (Li et al., 2020c,[Li et al., 2020d] d) with chronic inflammation and pyroptosis (Tian et al., 2020). The expression of ACE2 was not substantially different and does not indicate any difference in the susceptibility to COVID-19 infection among normal individuals and COPD asthma patients. However, persons with underlying lung disorders may be at higher risk for severe chronic airway disease or death (Guoping Li et al., 2020c). The exact mechanism and molecular interaction (including the various other proteins and cofactors) need to be focused during the interaction of SARS-CoV-2 with the lungs.

1.6. COVID-19 and heart

However, COVID-19 has reported significantly causing heart failure and death to persons with no signs of respiratory distress, regardless of harmful pre-cardiovascular disease (Madjid et al., 2020). SARS-CoV-2 induces direct insult to myocardial cells and their dysfunction (Clerkin et al., 2020; Ma et al., 2020) (Table 1). In Wuhan, China, 52 patients (27.8 %) out of 187 patients had the history of myocardial injury with elevated Troponin T (Guo et al., 2020b) and six patients (15 %) out of 41 patients had cardiovascular illnesses (Huang et al., 2020). The level of plasma Troponin demonstrates a significant linear correlation for the levels of C-reactive protein and N-terminal pro-brain natriuretic peptide. In early and rapid diagnosis, cardiac Troponins can play an additional role in managing and categorizing the significant risk in cardiac patients and deciding on their emergency or surgical intervention care (Rajappa and Sharma, 2005). In COVID-19 patients, cardiovascular markers such as Creatine kinase, Creatinine, Troponin I (cardiac), Brain Natriuretic Peptide, Lactate dehydrogenase, along with Alanine aminotransferase, Aspartate aminotransferase, and D-dimer concentration were markedly elevated (Chen et al., 2020c). Myocardial injury in COVID-19 may also result from cardiac dysfunction and arrhythmias (Guo et al., 2020b). As compared to lungs, the heart is the second major organ reported to get highly affected by SARS-CoV-2 entry via SARS-CoV-2 spike protein with ACE2, widely expressed in the heart and lungs (Zou et al., 2020). SARS-CoV-2 invades myocardial cells in the heart through ACE2, probably through pericytes resulting in increased macrophage infiltration, capillary endothelial cell dysfunction, and decreased ACE2 expression. The persistent increase in inflammatory cytokines following infection with COVID-19 may eventually lead to a reduction in coronary blood flow, oxygen supply, microthrombogenesis, and degradation of the coronary plaque (Guo et al., 2020b) pays the way to myocardial injury and failure. Cytokine storms and hyper inflammation will further aggravate the above responses (Akhmerov and Marban, 2020).

ACE2 interaction in heart: The severity of the COVID -19 outbreak is attributed primarily to viral spike protein interaction with host cells through ACE2 receptors that are highly expressed in the heart and lungs (Zhou et al., 2020a,b). Concerning viral load and subsequent incubation period (4–14 days), COVID-19 results in mild to severe symptoms associated with respiratory distress and heart failure (Lauer et al., 2020). SARS-CoV-2 once targets with ACE2, might elevates the production of angiotensin II level through the action of NADPH oxidase activity (Rukavina Mikusic et al., 2014); and may lead to endothelial dysnfunction along with chronic myocardial hypoxia.

Cytokine storm and nitric oxide (NO: The effect of COVID-19 on the cardiovascular system could be further enhanced by an ACE2 deficiency correlating with reduced bioavailability of nitric oxide and an eNOS expression in the aorta (Rabelo et al., 2016) to control homeostasis of blood pressure and vascular injury. The elevated angiotensin II that stimulates the production of cGMP degrading phosphodiesterases results in decreased bioavailability of cGMP and cause vascular dysfunction and injury (Stegbauer et al., 2013). However, the SARS-CoV-2 contribution and percentage towards myocardial injury via direct viral invasion or indirect systemic toxicity to multiple organs remains indistinct irrespective of the morbidity.

Therefore the harmful effects of COVID-19 on the heart will be mediated by SARS-CoV-2 viral load after its entry through the lungs (primary route). However, the COVID-19 manifestation on the myocardial damage and cardiovascular homeostasis either directly or

indirectly remains elusive regardless of the morbidity.

1.7. COVID-19 and liver

Liver, a large metabolic organ that is continuously exposed to dietary antigens, viruses and has recently reported to have varying degrees of damage in patients with COVID-19 (Table 1) With an Increases in Alanine aminotransferase (ALT) or Aspartate aminotransferase (AST), followed by slightly elevated levels of bilirubin with or without mechanical ventilation (Gu et al., 2020; Zhang et al., 2020a,b,c,d,e,f; Zhang et al., 2020a,b,c,d,e,f).). In COVID-19 patients, it is unclear whether the liver damage is caused by viral manifestations in liver cells or by the induced medication. ACE2 receptor in the target cell is the key binding site for SARS-CoV-2 virus, but the only medium expression of ACE2 in the liver is confirmed(Li et al., 2020f)); however, bile duct cells (cholangiocytes) have highly enriched ACE2 receptors, which may support viral binding and derangements of liver function (Chai et al., 2020; Hoffmann et al., 2020).

In contrast, immune responses to viral infection triggered by either immune interference or collateral damage to cytotoxic T cells and Kupffer cells in the liver may cause liver damage with no viral load (Bangash et al., 2020). Non-specific inflammatory markers such as elevated neutrophil and neutrophil to lymphocyte counts (virus-induced cytokine storm), coagulation and fibrinolysis pathway activation in response to sustained inflammation, high levels of ferritin reflect the involvement of hepatic cells (Bai et al., 2020) (Table 1). Also, a phenomenon called 'bystander hepatitis' that raises transaminases (AST and ALT) and circulatory cytokines may imply general immune stimulation or inflammation in systemic viral infections without compromising the function of the liver (Boettler et al., 2020) (Table 1). Uncertainly, COVID-19 infected patients with hepatotoxicity or liver injury may be due to antibiotics, antivirals and steroid medicines (Xu et al., 2020a,[Xu et al., 2020b] b,c,d,e,f,).

We consistently indicate that liver injury in COVID-19 may be the direct insult to the liver or bile cells via receptors of ACE2. It is further aided by hyper inflammation, cytokine storm or bystander hepatitis and drug-induced damage. In COVID-19 diagnosis and management, patients already with comorbidities such as liver damage are recommended to treat with hepatoprotective medicines for better progress and outcome. We required further research to elucidate the effect of COVID-19 on the liver.

1.8. COVID-19 and kidney

A recent study of COVID-19 on kidney dysfunction (Table 1) reported proteinuria, elevated markers of blood urea nitrogen, plasma creatinine, uric acids, and D-dimer (DD), (Li et al., 2020h). Contrary to the study, kidney damage is rare in COVID-19 patients (Wang et al., 2020b). Transmembrane protease serine 2 (TMPRSS2) is essential for the entry and spread of SARS-CoV-2 after interaction with the ACE2 receptor. TMPRSS2 gene expression mainly found in podocytes and proximal straight kidney tubule cells support SARS-CoV-2 entry into host cells (Xu et al., 2020a,[Xu et al., 2020b] b,c,d,e,f,). Histopathological findings and observation indicate the diffuse acute proximal tubular injury with loss of brush border in COVID-19 patients (Li et al., 2020h). SARS-CoV-2 also attacks the target cells via CD147 which is highly expressed on the surface of proximal tubular epithelial cells and plays a vital role in viral replication leads to dysregulated cell cycle and mediating the immune-inflammatory responses (Wang et al., 2020a).

Cytokine storm and Organ crosstalk: Cytokine storm, otherwise called cytokine release syndrome, had been documented since the onset of COVID-19 infection (Wu et al., 2020a). High levels of IL-6 in cytokine release syndrome may cause kidney damage. Possibly other various strategies towards kidney injury could be organ (Lung-kidney) crosstalk; inflammatory reactions and substances subsequently released lung damages could harm the kidney. Alternatively, kidney epithelial cell injury also caused severe lung damage and other organs (Ronco and Reis, 2020). COVID-19 patients with acute kidney injury had higher mortality risk (5.3 times) than those without acute kidney injury, and chronic disease patients had moderate mortality risk (1.5 times) (Li et al., 2020h). Therefore, monitoring the functions of the kidneys in COVID-19 patients regardless of chronic comorbid disease is equally important to reduce the risk of mortality and for improved outcomes. Patients need personalized medicine and differential management from the clinicians irrespective of the conditions; therefore, an in-depth understanding of cardiopulmonary physiological interactions in COVID-19 patients is crucial for effective management.

We have précised concepts that link the pathogenesis of kidney dysfunction in COVID-19 infection. Renal tubular epithelial cells, organ crosstalk, and cytokine storm are the existing possible potential involvement in kidney damage and are strongly interrelated. It is hoped that baseline existing understanding will lead to earlier diagnosis, recognition, and treatment in the future to improve the outcomes of COVID-19 patients.

1.9. COVID-19 and brain

Reports of 'Neuro−COVID-19 units show a common occurrence of neurological symptoms in COVID-19 patients (Talan, 2020) (Table 1). Symptoms of brain dysfunction such as headache, distressed consciousness develop in 40 % of patients with COVID-19 (Mao et al., 2020). SARS-CoV-2 in cerebrospinal fluid of infected patients suggests viral encephalitis (Cai et al., 2020). In a few patients, even with neurologic symptoms, develop symptoms associated with COVID-19 (Mao et al., 2020).

Brain invasion through the olfactory pathways:

The olfactory dysfunction such as loss of taste or smell among COVID-19 patients suggests that viruses infect the olfactory neuron (Giacomelli et al., 2020; WM, 2020.) similar to SARS-CoV and MERS-CoV(Mao et al., 2020; Wu et al., 2020a). SARS-CoV-2 may spread to the central nervous system (CNS) as the cribriform plate near the olfactory bulb, and the frontal lobes of the brain are close to the olfactory bulb neurons. Previous research on mice (Bohmwald et al., 2018) stated that removing the olfactory bulb limited the invasion of the coronavirus into the CNS that supports our argument. The other possible route of SARS-CoV-2 attack may be the presence of ACE2 has reported that removal of the olfactory bulb restricted the invasion of the coronavirus into the CNS, and this supports our argument. The other possible route of invasion of SARS-CoV-2 could be ACE2 receptors in mucosal epithelial cells of the oral cavity (Xu et al., 2020a,[Xu et al., 2020b] b,c,d,e,f,).

Bain invasion through an ACE2 receptors: ACE2 is identified as the acting receptor for SARS-CoV-2, and present in multiple human organs, including the nervous system (Hamming et al., 2004). The detection of ACE2 receptors over glial cells and other neurons, making them a potential target for SARS-CoV-2 (Baig et al., 2020) and this can also disrupt the blood-brain barrier by disrupting the vascular system and reaching the CNS. COVID-19 can potentially damage the capillary endothelium within the brain and contribute to elevated blood pressure. The risk of SARS-CoV-2 cerebral haemorrhage through an ACE2 receptor can result in abnormally high blood pressure and increase cerebral haemorrhage (Wu et al., 2020c).

Bain invasion through an inflammatory response: COVID-19 is currently believed to lead neurological diseases in concert with host immune mechanisms. After infection, a neurotropic virus (COVID-19) can activate glial cells and induce a pro-inflammatory condition (Li et al., 2020g) with release of a higher cytokine level such as IL-6, IL-2, IL-7, IL-10, GSCF, IP10, MCP1, MIP1A, and TNFα (Huang et al., 2020; Wan et al., 2020) accompanied by cytokine storm (Chen et al., 2020a; Mehta et al., 2020) that may be one of the risk factors for acute cerebrovascular disease and acute necrotizing encephalopathy.

Bain invasion via *hypoxia:* The fact that patients with COVID-19 frequently suffer from severe hypoxia (Guo et al., 2020c) can result in

hypoxic injury causing subsequent damage to the nervous system if it deteriorates rapidly. Infection with SARS-CoV-2 induced hypoxemia and excessive secretion of inflammatory cytokines which contribute to ischemic stroke incidence and development (Li et al., 2020e). Also, the roles of aging, oxidative stress, endothelial dysfunction, inflammation status, and other vascular risk factors may contribute to stroke (Ham and Raju, 2017; Regenhardt et al., 2018). Rather than physical suffering, patients experience psychological stress, anxiety, and lack of sleep due to social distancing and isolation treatment (Liu et al., 2020a).

Therefore, it is too recent to generate statistical evidence, and epidemiology of COVID-19 concerning CNS remains to be learned. Muscle relaxation has a positive effect on improving sleep quality and reducing anxiety (Polak et al., 1998). The widespread deregulated cellular homeostasis of COVID-19 patients caused by pulmonary, renal, cardiac, and circulatory damage could complicate and manifest into various neurological complications yet to be learned.

1.10. COVID-19 and GIT

The extrapulmonary manifestation of COVIDd-19 unfolds the symptoms of disease in digestive system. Includes nausea, vomiting, diarrhoea, abdominal pain and other nonspecific GI illness (Cipriano et al., 2020; Gu et al., 2020; Zhang et al., 2020a,b,c,d,e,f) (Table 1). The finding of SARS-CoV-2 RNA in the stool sample, has gained much attention from clinicians and researchers towards GI inspection, symptoms and analysis (Tang et al., 2020a; Xiao et al., 2020a)(Table 1). In cancer patients COVID-19 was reported to have a higher risk (Liang et al., 2020).

Laboratory report of COVID-19 patients with digestive symptoms showed higher liver enzymes, decreased monocytes, prolonged prothrombin time, and received additional antimicrobial management than patients with no digestive symptoms(Pan et al., 2020). Interestingly, the presence of a virus among patients with confirmed SARS-CoV-2 is recorded in stool samples (Zhang et al., 2020a,b,c,d,e,f), from anal and rectal swabs (Holshue et al., 2020; Tang et al., 2020a; Young et al., 2020) even after the clearance of virus in the respiratory tract (Cipriano et al., 2020). It was also persistently positive on rectal swabs in 8 out of 10 paediatric patients, even after negative nasopharyngeal swabs tests (Xu et al., 2020a,[Xu et al., 2020b] b,c,d,e,f,).

The gastrointestinal symptoms and virus involvement (in the faecal sample and anal/rectal swab) may be related to the significant involvement of ACE2 receptor in the glandular cells of the gastric, duodenal and rectal epithelium of the COVID-19 patients. This predicts the infected virions secreted from the GI cells of COVID-19 patients and consequently supports the fecal-oral transmission possibility of the virus in unhygienic practices. COVID-19 may damage the gastrointestinal system directly or indirectly through the chain reaction mediated via inflammatory and viremia, as viral RNA is detected in stool samples up to 53.4 % of patients (Tang et al., 2020a). Based on the above evidence, initial gastrointestinal symptoms in COVID-19 patient needs attention and notable. As it is highly involved in the community spreading and transmission, SARS-CoV-2 influence on GIT must be incorporated in early screening, detection, awareness, diagnosis, safety precautions, patient isolation, and early non-invasive diagnostic tool as much as respiratory symptoms are given importance. The extrapulmonary presentation of COVID-19 manifests the signs of illness within the digestive system, includes nausea, vomiting, diarrhoea, stomach pain and other nonspecific GI disorders (Cipriano et al., 2020; Gu et al., 2020; Zhang et al., 2020a,b,c,d,e,f)(Table 1).

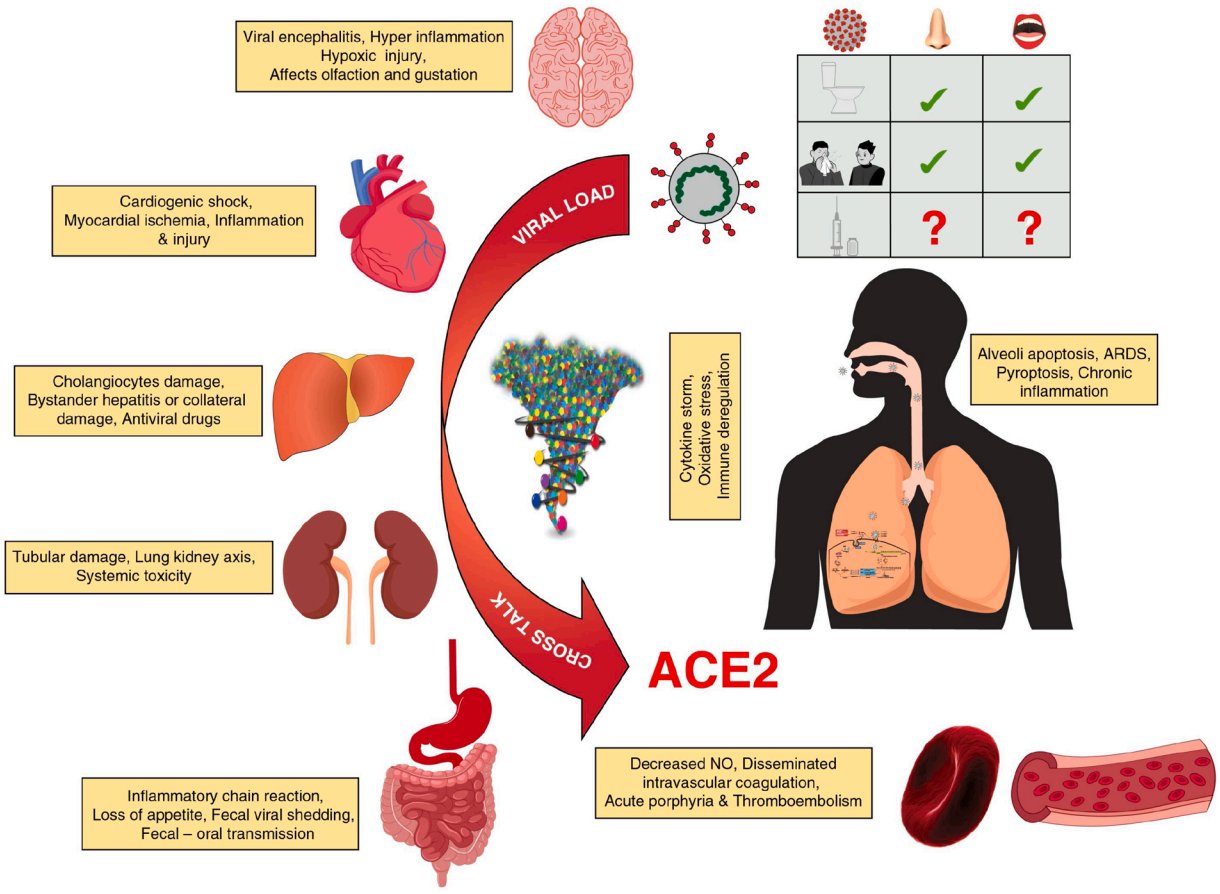

Fig. 5. SARS-CoV-2 and its viral load leading to various effects on vital organs through ACE2, in addition to cytokine storms, organs cross talk and systemic inflammation.

Table 2
Previous studies proceeding COVID 19 with multiorgan failure.

Review article	COVID-19 impact on multiorgan	Involvement of multiorgan has been linked with COVID-19. Comorbity and severity of extra pulmonary organs damage is notable and requires attention	(Zaim et al., 2020)
Correspondence	Attention must be taken of COVID-19 patients with comorbidity	Classification of COVID-19 patients based on diseases and disorders that are useful in triage management and treatment systems	(T. Wang et al., 2020a)
Research article	To determine the pathological changes in organs systems and the clinicopathological basis for serious and fatal effects.	Serious pulmonary damage and changes can appear related to multi-organ failure	(Lax et al., 2020)
Clinical trial	COVID-19 organ dysfunction and mechanism	Ongoing (ends 2021)	NCT04316884
Review	Strategy for handling COVID-19 critically ill patients	Multiorgan functions and inflammatory status must be monitored	(Shen et al., 2020)
Correspondence	Endothelial status in COVID-19	Viral elements and inflammatory cells in the causes of endothelium apoptosis and pyroptosis	(Varga et al., 2020)
Article	Proposing inhibition of the complement pathway for preventive, management and treatment of multi-organ damage in COVID-19	Unhindered complement system activation caused by COVID-19 associated with multi-organ failure.	(Noris et al., 2020)
Article	COVID-19 pathogenesis and multiorgan damage	AGTR2 may be a new target for treatment of COVD-19 patients	(L. Guo et al., 2020a)
Article	Assessing the relationship and potential function between COVID-19 and multiple organ failure other than pneumonia	The direct viral impact via ACE2 may be injury to the other organs	(Yang et al., 2019)
letter to editor	Laboratory analysis of 25 fatal cases of COVID-19.	Multiple organ failure syndromes is the leading cause of COVID-19 mortality most frequently observed in older male comorbidities patients.	(Tu et al., 2020)

1.11. COVID-19 and RBC accompanied by thromboembolism

In COVID-19 cases, sepsis is one of the most expected outcomes (Zhou et al., 2020a,b), suggesting RBC involvement in COVID-19 infection (Lippi and Plebani, 2020). Hyperbilirubinemia, increased serum ferritin levels, decreased RBC as well as hemoglobin may indicate the hemolysis and development of haemolytic anaemia (Wu and McGoogan, 2020) or acute porphyria in COVID-19 cases (Abrahams, 2020; Chen et al., 2020b; Menk et al., 2018; Zhang et al., 2020a,b,c,d,e,f) (Table 1). Bioinformatics analysis has found that SARS-CoV-2 glycoproteins such as orf1ab, orf10, and orf3a attacks 1beta chain of haemoglobin open reading frame 8 (ORF8) that binds to the porphyrin of haem and displaces iron (Wenzhong and Hualan, 2020). In general, SARS-CoV-2 may not be considered to be the first known virus to alter porphyrin metabolism; hepatitis C virus (Hep C) and human immunodeficiency virus (HIV) infection also contribute to a non-acute form of porphyria(Wenzhong and Hualan, 2020). Porphyria is the disorder related with heme biosynthesis pathway and loss of autonomic control of breathing and autonomic neuropathy is a clinical feature of acute porphyria (Tracy and Dyck, 2014).

Report on the relation between the ABO blood group and SARS-CoV-2 susceptibility to increased risk of COVID-19 infection among people with blood group A relative to other blood group (Zhao et al., 2020). In patients affected by COVID-19, haemostatic abnormalities such as disseminated intravascular coagulation and pulmonary embolism have been reported (Han et al., 2020; Le Berre et al., 2020; Tang et al., 2020b). Most haemostatic abnormalities may occur due to increased D-dimer (Lippi and Favaloro, 2020), thrombocytopenia (Wong et al., 2003), prolonged prothrombin time (Le Berre et al., 2020), thrombin time (Han et al., 2020), elevated fibrin/fibrinogen degradation products and decreased activated partial thromboplastin time (Han et al., 2020).

Hence, depending on the available reports, we have speculated that the primary pathogenic mechanism of COVID-19 does not only confide with lung. However, sepsis, acute porphyria, disseminated intravascular coagulation, and interaction of SARS-CoV-2 surface glycoprotein with 1-beta chain of haemoglobin (Wenzhong and Hualan, 2020), is often the secondary complications observed in COVID-19 patients.

2. Conclusion

This review concluded (Fig. 5) that SARS-CoV-2 is intervened mainly through ACE2 receptor and other cofactors, mainly TMPRSS2 in the lung and further progress to pneumonia and ARDS. However, depending on viral load and regulated by the ACE2 receptor, an infection may further spread to other organs such as heart, liver, kidney, Brain, endothelium, GIT, immune cell, and RBC thromboembolism. This may follow with cytokine storm with an extensive discharge of proinflammatory cytokines from deregulating the immune system. This overall cytokine results in systemic inflammation and organ crosstalk resulting in multiorgan failure (Fig. 1, Table 2). This finding may lead the clinician and scientist to the diverse approach to fight with COVID-19. More attention and studies are required to understand the involvement of diverse factors and possible reasons for organ crosstalk in COVID-19 to prevent multiorgan failure syndrome and mortality in the near future.

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Declaration of Competing Interest

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