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Mechanisms of COVID-19-induced cardiovascular disease, is sepsis or exosome the missing link?

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Abstract

COVID-19 (Coronavirus disease 2019) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has reached a pandemic level, spreading across the globe by affecting over 33 million people and causing over 1,009,270 deaths. SARS-CoV-2 is highly infectious with a high basic reproduction number (R_0) of 2.2–5.7 that has led to its exponential spread and very little is known about it in terms of immunogenicity and its molecular targets. SARS-CoV-2 causes acute respiratory distress syndrome, followed by multiple organ failure and death in a small percentage of individuals. Cardiac injury has emerged as another dreaded outcome of COVID-19 complications. However, a thorough understanding of the pathogenesis of SARS-CoV-2 is lacking. In this review, we discuss the virus, possible mechanisms of COVID-19-induced cardiac injury, potential therapeutic strategies, and explore if exosomes could be targeted to treat symptoms of COVID-19. Furthermore, we discuss the virus-induced sepsis, which may be the cause of multiple organ failure, including myocardial injury.

Keywords

COVID-19; SARS-CoV-2; Sepsis; Exosomes; Cardiovascular disease

Introduction

Coronavirus disease 2019 (COVID-19), caused by the SARS-CoV-2 virus, was first reported in December 2019, with the first likely case recorded in Wuhan, China (Lescure et al., 2020). Since this time, the virus has spread to more than 200 countries, with over 33 million confirmed cases and 1,009,270 deaths as of October 1, 2020 (https://covid19.who.int/). COVID-19 is thought to spread mainly through respiratory droplets and close contact, and displays a relatively high R_0 value estimated between 2.2–5.7, and this high infection potential combined with a delay in visible symptoms for up to 2 weeks has enabled this virus to spread rapidly into pandemic proportions (Cui et al., 2019; Sanche et al., 2020).

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Due to these extreme circumstances, great effort has been made into developing diagnostic tools and treatment options for the virus. At the time of this writing, RT-qPCR-based assays are the diagnostic standard for coronavirus testing; however, immunoassays and other technologies are rapidly being developed and deployed (Cheng et al., 2020). Data from testing suggest that age and the presence of comorbidities, which include cardiovascular disease, obesity, cancer, and diabetes are major risk factors in COVID-19 fatality (Onder et al., 2020). These risk factors pose major challenges to COVID-19 treatment, as increased isolation and more stringent testing and therapeutics are necessary in the case of comorbidity (Wu et al., 2020).

The virus itself poses major clinical challenges. It has created a large patient load that threatens to overwhelm healthcare systems and treatment demands, the use of critical supplies, such as ventilators, large scale PPE usage, and basic medical supplies (Ranney et al., 2020). The concurrent disruption of global supply chains furthers this critical need. Along with the equipment challenges, the immediate patient burden stretches all normal supplies thin and limits healthcare availability for the general population and prevents non-critical surgeries from being performed due to the risk of contamination (Cohen et al., 2020). These challenges make it critical for effective clinical treatments to be developed, to lessen the burden on stressed healthcare systems (Hatswell, 2020). In this review, we describe in brief about the virus properties, COVID-19 pathogenesis specifically focusing on sepsis and heart, and available treatment options.

SARS-CoV-2 infectivity characteristics

SARS-CoV-2 is an enveloped, single-stranded, positive-sense RNA virus (Figure 1) that belongs to the beta-coronavirus family of viruses and is capable of infecting humans and animals (Shereen et al., 2020). Several members of this virus family have been known to infect humans with mild symptoms and are self-limiting (Andersen et al., 2020). Interestingly, SARS-CoV-2 is closely related to SARS-CoV (severe acute respiratory syndrome virus-82% homology) and MERS-CoV (Middle Eastern respiratory syndrome virus-50% homology) that cause respiratory disease and were responsible for outbreaks in 2003 (China) and 2012 (Middle East), respectively. While the evolution of these viruses has become a very hot topic, these viruses undergo gene recombination, insertions, and deletions, making them easy to mutate, manipulate, and transmit from one species to another (Luo et al., 2018). Consistent with the above report, several studies using *in vitro* cell culture and mouse models have shown the potential for the emergence of COVID-like viruses (Menachery et al., 2015).

Virus gains entry inside the cell through Angiotensin-converting enzyme 2 (ACE2) receptors (Lan et al., 2020; Wan et al., 2020). Once inside the cells, its RNA is released, transcribed to virus proteins (mainly nonstructural proteins). In the late phase, virus structural proteins are transcribed that are used for virus repackaging and release (Figure 2) (Shereen et al., 2020). There are several important characteristics of this virus that make it unique. (1) It is an enveloped virus with a lipid bilayer, therefore, making it very stable in the environment (72 hours on plastic and 3 hours in aerosols) (van Doremalen et al., 2020) and also easy to inactivate using routine sanitizers; (2) The virus is highly infectious. This increase in

infectivity is due to unique sequences in the spike protein that enhances its affinity to its receptor by several-fold (discussed below); (3) Virus is present in the saliva of infected individuals and therefore present in the droplets while talking and singing aloud, coughing, and sneezing; (4) It is less pathogenic, thus 25–50% of people are asymptomatic; (5) This virus can infect animals (mainly cats) as well. Therefore, it poses a major challenge for preventing virus spread.

As mentioned above, virus spike protein is very key to its infectivity. Virus genomic sequence analysis has identified several insertions and mutations in the spike gene, therefore, it may have diverged from other related viruses, such as SARS-CoV, MERS-CoV, RaTG13, and Pangolin coronavirus (Andersen et al., 2020). Interestingly, structure-function analysis by crystallography and binding studies has identified that SARS-CoV-2 spike protein has a very high affinity for ACE2 receptor (10–20 fold higher than SARS-CoV) (Wrapp et al., 2020). Also, insertion of 4 amino acids (RRAR) in the spike gene at S1-S2 junction is targeted by host furins and transmembrane protease serine 2 (Figure 1), and other proteases that promote virus fusion, and therefore increase the infectivity of the virus (Coutard et al., 2020; Hoffmann et al., 2020). Interestingly, the presence of these motifs has been associated with increased pathogenicity in several viruses, including H5N1, MERS, and others (Coutard et al., 2020). It is also intriguing that even with high sequence homology, similar structure, and affinity for the ACE2 receptor between SARS-CoV and SARS-CoV-2 spike protein, none of the antibodies available for the SARS spike protein can neutralize SARS-CoV-2 virus (NIH). This could be largely due to the insertion and several other mutations in the SARS-CoV-2.

Pathogenesis of COVID-19: The sepsis link

COVID-19 is a highly contagious respiratory syndrome and can cause multi-organ failure that can lead to death in a small percentage of infections. It is transmitted from person to person by direct contact, through droplet infection, fecal-oral transmission, and aerosol. The virus can replicate in a wide range of cells that express ACE2, including nasal epithelium, nasopharynx, upper respiratory tract, type II pneumocytes in the lung, gastrointestinal (GI) tract, immune cells, and endothelium (Kumar et al., 2020; Sungnak et al., 2020). Because of the wide range of target cells, pathological symptoms and lesions are spread across different organs (Table 1). The severity of the disease also depends on risk factors and pre-existing health conditions. Advanced age is a major risk factor followed by hypertension, diabetes, obesity, chronic respiratory conditions, including chronic obstructive pulmonary disease (COPD) and asthma, heart diseases, and immune status (Fang et al., 2020; CDC). In the United States, African Americans are affected disproportionately compared to other races. However, underlying mechanisms are unknown. A recent study identified extensive pulmonary thrombosis, microcoagulopathy in small vessels, hemorrhage, diffuse alveolar damage accompanied by intracardial necrosis and right ventricle dilation among African Americans during autopsies (Fox et al., 2020). These findings were consistent with other studies, therefore pre-existing cardiac risk factors have been suggested to be the possible causes (McGonagle et al., 2020). However, African Americans have higher incidence of several health conditions such as hypertension, obesity and diabetes, which are known risk factors for heart diseases and therefore might be prone to severity of the disease.

Interestingly, A proarrhythmic variant p.Ser1103Tyr-SCN5A is highly prevalent among African Americans, which is associated with ventricular arrhythmia sudden cardiac death under hypoxic conditions may also be responsible for increased fatalities (Giudicessi et al., 2020). Also, human leukocyte antigen (HLA) gene and ACE2 gene polymorphisms (Hussain et al., 2020) have been suggested to affect the severity of the disease.

ACE2 signaling has also attracted a lot of attention given the fact that the ACE2/$Ang_{1–7}$/Mas axis is crucial in regulating blood pressure, inflammation, fibrosis, and thrombosis, etc. (Santos et al., 2003; Simões e Silva et al., 2013). As a key mode of internalization, downregulation or shedding of ACE2 after the virus entry has been reported in SARS-CoV (Glowacka et al., 2010; Kuba et al., 2005), NL63 (Dijkman et al., 2012), and H5N1 (Zou et al., 2014), and a similar outcome is speculated in the SARS-CoV-2 infection. Downregulation of ACE2 in the infected organs could interfere with the ACE2/$Ang_{1–7}$/Mas axis, resulting in activated AngII and Renin-angiotensin-aldosterone system (RAAS), which is supposedly one of the plausible causes of COVID-19-associated alveolar inflammation and lung injury (Kai & Kai, 2020; Verdecchia et al., 2020).

After entry through ACE2 receptors, the virus sheds its genome into the cytoplasm, which is transcribed to early viral proteins that play a critical role in the suppression of host immune response, tissue damage, and enhance viral genome replication. Structural proteins are transcribed in the late phase of viral replication to repackage and release virus particles (Figure 2). Interactome analysis of all the viral proteins has revealed that viral proteins target host cell nuclear export, integrated stress response system, RNA processing, mitochondrial functions, and cell death signaling (Gordon et al., 2020). During the virus replication, host cells activate anti-viral immune response through MHC class I antigen presentation. This is followed by either an effective immune response to clear the virus infection or immune dysregulation that leads to a severe form of the disease. An effective anti-viral response involves activation of both (i) cell-mediated antiviral immunity through activation of CD8+ T cells, natural killer (NK) cells, and monocytes that target virus-infected cells and (ii) humoral immunity mediated by production of virus-neutralizing antibodies, such as IgG and IgM by $CD27^{hi}CD38^{hi}$ cells, activated ICOS + PD-1+ follicular helper T cells- T_{FH} cells ($CD4^+$ and $CXCR5^+$ cells) (Figure 3) (Thevarajan et al., 2020).

In individuals who do not recover, come down with acute respiratory syndrome, hypotension, and multiple organ failure (Xu et al., 2020). Laboratory findings showed high levels of fibrin degradation product D-dimer (indicative of abnormal clotting) (Zhou et al., 2020), lymphopenia (decrease in the number of lymphocytes) (Chan et al., 2020), increased neutrophil count (Liu et al., 2020), and cytokine storm (Mehta et al., 2020) that is suggestive of sepsis. Interestingly, the culture of lung fluids did not yield bacterial growth (Fox et al., 2020; Li et al., 2020). Therefore, sepsis is likely caused by the virus itself (Li et al., 2020) that might leads to (i) immune dysregulation leading to cytokine storm, (ii) respiratory dysfunction leading to hypoxemia, and (iii) metabolic acidosis due to circulatory dysfunction (Figure 3). Cytokine storm is characterized by increased production of cytokines, mainly IL-6, C-reactive protein (CRP), TNF-α, IL-1β, IL-33, IFNγ, GMCSF, and others (Mehta et al., 2020). In addition, virus-infected cells (type II pneumocytes, endothelial cells, etc.) could be the source of cytokines and toxins. Virus particles have also

been demonstrated in endothelial cells from blood vessels (Varga et al.,2020) that may be responsible for microvascular dysfunction. Therefore, it is hypothesized that virus-induced endothelial dysfunction may be promoting disseminated intravascular coagulation that limits blood flow and prevent oxygenation in the lungs (Figure 3). Hypoxia, due to an acute respiratory syndrome, along with metabolic acidosis due to poor circulation and microvascular dysfunction, may partly explain the cause of multiple organ dysfunction (such as heart, kidney, and liver) (Figure 3). However, the cause and sources of cytokine storm, lymphopenia, and abnormal clotting are not known; although activated immune cells, lymphocyte exhaustion has been suggested (Zhou et al., 2020). However, it should be noted that cytokine storm is also observed in SARS and MERS infections. While in SARS it is attributed to exaggerated cytokine production by virus-infected alveolar endothelial cells, dendritic cells, and macrophages; in MERS it is attributed to lung infiltrating neutrophils, macrophages, and peripheral blood mononuclear cells (Channappanavar & Perlman, 2017). Interestingly, transcriptomic analysis of bronchial alveolar fluid, peripheral blood mononuclear cells from COVID-19 human patients and ferret models and invitro cell lines revealed poor antiviral responses lacking IFNI and III responses (Blanco-Melo et al., 2020; Gardinassi et al., 2020), which may partly explain asymptomatic and prolonged infection. These studies also revealed interferon-specific gene signatures, activation of neutrophils, and poor response from dendritic cells and macrophages. Furthermore, recent studies by different groups showed presence of reactive T cells to SARS-CoV-2 peptide antigens in people who have not been infected with virus, and has been attributed to exposure to corona viruses that cause common cold (Grifoni et al., 2020; Moreno et al., 2020; Premkumar et al., 2020). However, their role in pathogenesis and development of immunity remains to be seen (Sette & Crotty, 2020). In addition, future research identifying the root cause of the cytokine storm will help treat COVID-19 complications. Likewise, the cause of the severity of the disease in the presence of other comorbidities is unknown. However, it is well known from the literature that inflammation is upregulated in most of these cardiovascular and metabolic diseases characterized by an increase in C-reactive protein, TNF-α, and IL-6 levels. Therefore, we speculate that the immune system is primed for overactivation under COVID-19 infection in these individuals.

Exosome link to COVID-19 Pathogenesis

Exosomes are nanoscale extracellular double-membrane vesicles secreted by cells that have emerged as novel intercellular communicators. Exosomes are actively secreted by endolysosomal system and carry messages in the form of proteins, enzymes, cytokines, lipids, and RNA from donor cells to the target cells. Extensive research has shown that exosomes play critical role in organ cross-talk, maintaining tissue homeostasis, host-pathogen interactions, and pathophysiology of various diseases including sepsis (Dykes, 2017; Kita et al., 2019; Sahoo & Douglas, 2014; Schorey et al., 2015). Likewise, virus infections exploit exosome pathway to gain entry, spread virus infection, virus packaging, evade host immune system, and pathogenesis (shown in Figure 4; and virus pathogenesis using exosomes is summarized in Table 2) (Alenquer & Amorim, 2015; Anderson et al., 2016; Urbanelli et al., 2019; Wurdinger et al., 2012). Due to similarities in pathways of exosome biogenesis (ESCRT-dependent and independent), their fate (actively taken up by target cells by endocytosis, pinocytosis, and receptor-mediated uptake) and virus uptake,

packaging, and release; they were likened to be relatives (Nolte-'t Hoen et al., 2016). Exosome-mediated host immune modulation by viral infections has been extensively studied and has been reviewed elsewhere in detail (Schorey et al., 2015). Virus infections stimulate host cells to secrete exosomes that function as pathogen-associated molecular patterns (PAMPS), carry inflammatory mediators, cause inflammation (Schorey et al., 2015). For example, exosomes from EBV-infected cells that are enriched in dUTPase induce activation of NF-κB pathway and stimulate macrophage cytokine release (Ariza et al., 2013). Likewise, HCV mRNA in exosomes induce secretion of IFN alpha from macrophages and exosomes from C3/36 cells infected with Zika virus induces expression TNF alpha from monocytes, cause endothelial damage to induce intravascular coagulation and inflammation (Martínez-Rojas et al., 2020). Exosomes from Kaposi sarcoma associated herpes virus also cause endothelial damage and induce expression of IL6 (Chugh et al., 2013). Exosomes from virus-infected cells also cause apoptosis of immune cells. For example, HIV infection induces secretion of exosomes that are enriched in viral Nef protein, which cause apoptosis of endothelial cells and CD4 T-helper cells (Lenassi et al., 2010). Likewise, EBV-infected cells secrete exosomes enriched with galactin9 that cause apoptosis of cytotoxic T cells specific to EBV-infected cells (Dukers et al., 2000). In summary exosomes from virus-infected cells can cause tissue injury by activating inflammation and cytotoxicity.

Several important features of SARS-CoV-2 infection, mainly hyper-activated immune system to induce sepsis-like disease characterized by cytokine storm and lymphopenia raises the question if exosomes are involved (Figure 4). This idea is further strengthened by TGN pathway (Trans-Golgi network, which is part of sorting system in endolysosomal pathway) involvement in replication of SARS-CoV-2. In addition, recent data showing involvement of lipid metabolism including cholesterol metabolism (Zhang et al., 2020) in the pathogenesis COVID complications poses the question if exosomes are involved in pathogenesis of SARS-CoV-2 infection. Consistent with this idea, SARS-CoV-2 protein interactome analysis revealed interaction with Rab proteins that are part of ESCRT pathway involved in exosome biogenesis. Interestingly, several viruses that exploit exosomes for pathogenesis interact with Rab proteins (Bello-Morales et al., 2012; Fraile-Ramos et al., 2010, p.; Gerber et al., 2015). Moreover, high throughput lipidomics of sera from human patients revealed exosome-specific lipid profiles that were enriched with sphingomyelins, gangliosides, and deficient in Di-acyl glycerols (DAG). Interestingly, exosome enrichment with gangliosides (GM3) was strongly associated with severity of the disease and likely cause of lymphopenia, since immune cells have preference for GM3-enriched exosomes which is cytotoxic (Song et al., 2020). It should also be noted that SARS-CoV-2 barely eight-month-old and its understanding is evolving; and given the lack of strong anti-viral immune response as discussed before, role of epigenetics mechanisms including miRs and other non-coding RNAs needs full investigation. Moreover, extensive literature suggests that exosomes play an important role in shuttling of these non-coding RNAs between different cell types and have been implicated in development of cardiovascular diseases. Interestingly, in a recent *in-vitro* study, transduction of lung epithelial A549 cells with SARS-CoV-2 structural and non-structural genes (excluding viral Spike protein) resulted in secretion of exosomes enriched with viral RNAs. These exosomes were successfully taken up by the human induced pluripotent stem cell-derived cardiomyocytes (hiPSC-CMs), which resulted in elevated

inflammatory markers in hiPSC-CMs along with presence of viral genes (Kwon et al., 2020), allowing us to speculate the possible role of exosomes in the SARS-CoV-2 pathogenesis. This may also explain the possible mechanism of myocardial inflammation in COVID-19 patients without direct viral infection that has puzzled the researchers. Consistent with this, given the extensive activation and inhibition of protein kinases by SARS-CoV-2 infection in cells (Bouhaddou et al., 2020), it is also possible that exosomes from virus-infected cells may also carry proteins that can activate inflammatory response and cause tissue injury in distant organs. Therefore, it will be interesting to see if exosomes can be targeted for therapy, and future research using the exosome research tools will be helpful in addressing these possibilities.

COVID-19 and Heart

Cardiac complications associated with COVID-19 infection

Although the lungs and the respiratory tract are the most vulnerable tissues for SARS-CoV-2 infection (Zou et al., 2020), the virus also severely affects the pathophysiology of the heart. Several cardiac complications are associated with SARS-CoV-2 infection, which is summarized in Table 3 and Figure 5. Here we discuss acute and chronic cardiac manifestations of COVID-19.

Direct myocardial injury: Myocardial localization of SARS-CoV-2

Due to the high abundance of ACE2, the heart is among high-risk organs (Chen et al., 2020; Zou et al., 2020) affected by COVID-19 and speculated to harbor SARS-CoV-2 RNA possibly due to extra-pulmonary dissemination of the virus. Reduced ACE2 expression has been negatively correlated with various cardiac pathologies, such as hypertension, maladaptive cardiac remodeling, heart failure, and cardiomyopathies (Zamaneh et al., 2009; Oudit et al., 2009; Patel et al., 2014; Patel et al., 2016), and as it is postulated that SARS-CoV-2 infection could result in ACE2 downregulation, this might affect the cardiac pathophysiology via differential regulation of ACE2/$Ang_{1–7}$/Mas axis. The relationship between SARS-CoV-2, ACE2, and cardiovascular outcomes has been reviewed recently and could help to expend the knowledge horizon (Junyi et al., 2020; South et al., 2020)

Direct cardiac injury by SARS-CoV-2 is debatable; however, the presence of ACE2 in the heart poses a strong possibility of internalization of COVID-19 by ACE2-expressing cells in the heart. Out of 44 patients that died from SARS, a study examined the presence of the SARS-CoV genome in the 20 autopsied heart tissues, and 7 of the samples (35%) were found positive for the viral RNA. Moreover, myocardial localization of the viral particles was attributed to the expression of ACE2 in the heart (Oudit et al., 2009). Concerning the current coronavirus pandemic, very few reports have been published to confirm the myocardial infiltration of the SARS-CoV-2. Tavazzi *et al.* (Tavazzi et al., 2020) reported the first case of myocardial localization of SARS-CoV-2 in a 69-year-old patient who was diagnosed with acute myocardial injury, hypotension, and cardiogenic shock. Endomyocardial biopsy of the patient showed a low-grade interstitial and endocardial inflammation along with virus particles present in the interstitial cells; however, the biopsy did not confirm the presence of coronavirus particles in cardiomyocytes or endothelial cells.

Myocardial localization of COVID-19 could imply the viremic phase or migration of infected macrophages to the heart and possibly other tissues. Exosome-mediated dissemination of SARS-CoV-2 and viral genome/protein could also be of scientific interest and requires further exploration. As discussed in the previous section, recent evidence also pointed towards the exosomal transfer of SARS-CoV-2 genes to cardiomyocytes, which resulted in increased inflammation in these cells (Kwon et al., 2020). Many viruses share common endocytic signaling mechanisms and have been shown to exploit the exosomal machinery for their transmission and infection (Alenquer & Amorim, 2015; Izquierdo-Useros et al., 2010; Ramakrishnaiah et al., 2013a). The field of SARS viruses is evolving and exploring the involvement of exosomes could help better understand the pathological mechanisms and develop therapeutics.

In another study, the postmortem pathological examination of the heart biopsies of COVID-19 patients (Tian et al., 2020) revealed focal edema, myocardial hypertrophy, and interstitial fibrosis; however, these features were linked to pre-existing cardiac conditions rather than acute injury due to COVID-19 infection. Even though no apparent infiltration of inflammatory cells was observed in the heart, the real-time PCR analysis showed the SARS-CoV-2 genome in one of the two heart biopsies. Overall, these findings indicate the existence of the SARS-CoV-2 (or its genome) in the heart, either through direct infection or disseminated by migrating cells or through exosomes, which might ultimately exert pathological changes in the myocardium. However, the lack of conclusive evidence necessitates further investigations to understand the direct effects of SARS-CoV-2 in the heart.

Role of inflammation in COVID-19 associated myocardial injury

Although direct myocardial injury via SARS-CoV-2 and ACE2 interaction is a strong possibility, COVID-19-associated cardiac damage is widely attributed to cytokine-inflicted systemic and tissue inflammation. Dissemination of the virus into circulation through infected macrophages and other immune cells could lead to an exaggerated immune response and multi-organ dysfunction. One of the early reports describing myocardial inflammation in SARS-CoV-2 infection reported fulminant myocarditis with elevated IL-6 levels along with other cardiac injury markers (troponin I, myoglobin, and n-terminal brain natriuretic peptide) (Zeng et al., 2020). Various cohort-based studies also showed increased cytokine production during COVID-19 infection, and cytokine storm in those patients was found to be associated with the disease severity and patient survival (Huang et al., 2020; Zhou et al., 2020a). Previously, it was found that immunological response in SARS-patients is mainly mediated through Th1-cell activity (Wong et al., 2004) as opposed to SARS-CoV-2 infection, where an imbalance between both Th1 and Th2 activity was found to aggravate the inflammatory surge (Huang et al., 2020). Overall, evidence from the published studies so far implies that the SARS-CoV-2-induced inflammatory surge is the plausible cause of organ damage in patients and could be targeted for therapeutic interventions.

Acute myocardial injury

In SARS-CoV-2 patients, myocardial injury is evident by several factors, such as an increase in myocardial injury markers, echo- and electrocardiographic abnormalities, cytokine storm, and myocarditis.

Acute myocardial injury has been a critical and persistent feature in COVID-19 patients. An earlier report showed that among 138 patients (Wuhan, China) admitted for SARS-CoV-2 infection, 7.2% of patients had acute cardiac injury (Wang et al., 2020), and cardiac injury was more prominent in the patients who needed ICU care than non-ICU patients. In another case, 82 out of 416 hospitalized COVID-19 patients (19.7%) had cardiac injury (Shi et al., 2020) with elevated high-sensitivity troponin I levels (median interquartile range 0.19 vs <0.006 μg/L in patients without cardiac injury). Cardiac injury patients also had a higher mortality rate than those without cardiac injury (51.2% vs 4.5%). A retrospective cohort study of 191 patients from Wuhan, China showed that 46% of non-survivors had high-sensitivity cardiac troponin I level above the 99th percentile upper reference limit as compared to 1% of survivors (Zhou et al., 2020). Increased levels of high-sensitivity troponin are reported in most of the COVID-19 patients with cardiac injury (Guo et al., 2020; Inciardi et al., 2020; Sala et al., 2020), making it a crucial diagnostic marker of myocardial injury in COVID-19 patients.

In addition to high-sensitivity cardiac troponin, N-terminal pro-brain natriuretic peptide (NT-proBNP) is another important biomarker for myocardial stress in patients infected with SARS-CoV-2. Brain natriuretic peptide (BNP) and NT-proBNP concentration increase in the circulation in response to cardiac impairment and changes in ventricle wall tension, and these molecules are widely used as biomarkers of heart failure (Bay et al., 2003; Hunt et al., 1997; Yasue et al., 1994). In the patients infected with coronavirus, increased concentration of NT-proBNP in circulation manifests myocardial injury and cardiac complications. A rise in NT-proBNP has been reported in severe COVID-19 cases associated with adverse clinical outcomes and poor prognosis (Gao et al., 2020; Guo et al., 2020; Inciardi et al., 2020; Zeng et al., 2020).

Laboratory findings also showed an elevation in other cardiac injury markers, such as creatine kinase, lactate dehydrogenase, and C-reactive protein in COVID-19 patients (Du et al., 2020; Inciardi et al., 2020; Sala et al., 2020).

Chronic cardiac damage in COVID-19 patients

There is a scarcity of data on the long-term implications of respiratory viruses associated with epidemics. Metabolic profiling of 25 SARS-CoV survivors in a 12-years follow-up study showed dyslipidemia, altered glucose metabolism, and cardiovascular abnormalities (Wu et al., 2017). Another cohort-based 10-years follow-up study showed an increased risk of cardiovascular complications in patients hospitalized for pneumonia (Corrales-Medina et al., 2015). Structural similarity between SARS-CoV and SARS-CoV-2 could predict long-term cardiovascular damage. The long-term effect of SARS-CoV-2 on the heart is addressed in two recently published German cohorts-based studies (Lindner et al., 2020; Puntmann et al., 2020). One study showed a high viral load of SARS-CoV-2 in the myocardium (above

1000 copies per μg RNA) of 41.0% of the patients (16 of 39 autopsied samples). However, this high viral load was not attributed to an inflammatory reaction as no inflammatory cell infiltration was observed (Lindner et al., 2020). Similarly, an unselected cohort of 100 recovered patients revealed that 78% of the recovered patients had myocardial abnormalities, including myocardial inflammation, regional scars, and elevated injury markers (Puntmann et al., 2020). These findings necessitate the urgency of large cohort-based follow-up studies on recovered patients to evaluate the long-term effect of SARS-CoV-2 on the cardiovascular system.

Potential therapeutic strategies against SARS-CoV-2 or its complications

For COVID-19 being an infectious disease, vaccination is the best choice to prevent infection. However, this virus is just 10-months old, therefore, vaccine production and their validation, in terms of safety and protection may take longer than expected time. Fortunately, several vaccines are in production, and early testing is in humans and macaques with RNA-1273 (Moderna), ChAdOx1 (Oxford), BNT162b2 (Pfizer), Ad26.COV2-S (Johnson and Johnson), and many others have shown promising results and are in advanced stages of clinical trials. Also, very little is known about the immunogenic antigen from SARS-CoV-2 that is important for activating protective immunity. Therefore, given the pandemic nature of COVID-19, current strategies involve repurposing of existing drugs to control infection in the body, and symptomatic treatments to mitigate the complications.

Antiviral therapy

SARS-CoV-2 emerged in December 2019; it is barely 10-months old, and there is a scarcity of data about the virus. Therefore, the current strategy has been repurposing of existing drugs on compassionate grounds to identify a drug that could help mitigate the virus infection. However, due to its close similarity with SARS and MERS viruses, several of the drugs that are in the pipeline for these viruses, as well as others like Ebola, have been used in clinical trials (summarized in Table 4, please note we have listed the drugs which are used alone or in combination). Data so far indicates that Remdesivir, a nucleotide analog (adenosine) that is incorporated into viral RNA and inhibit its replication, has promising results in patients that are treated with the drug at a very early stage of infection (2–3 days of infection). Interestingly, Remdesivir was originally developed to treat Ebola virus infection. Therefore, the repurposing of existing drugs is a way forward to find quick and timely treatment options. Also, the SARS-CoV-2 protein interactome analysis has identified several targets for which there are drugs available in the developmental stage, which could provide novel avenues to treat virus infection (Gordon et al., 2020). Likewise, high throughput quantitative mass spectrometry-based phospho-proteomics analysis of SARS-CoV-2-infected Vero E6 cells identified strong activation of p38 MAP kinases, casein kinase II (CK2), Ca^{++} and calmodulin-dependent kinases, PRKG1/2, and inhibition of cell cycle and cell growth kinases (Bouhaddou et al., 2020). Interestingly, inhibition of p38 MAP kinases, cyclin-dependent kinase (CDK), AXL, and PIKFYVE kinases inhibited virus replication in Vero and A549 cell lines (Bouhaddou et al., 2020), providing novel targets for antiviral drug development. In addition, monoclonal antibodies neutralizing virus are also being developed and being tested. Antiviral immunotherapy using INF-β as an aerosol in combination with lopinavir-ritonavir and ribavirin has also shown promising results in small trial. The triple

therapy was effective in clearing the virus within 8 days from most of the patients (Hung et al., 2020). This may partly be explained by poor antiviral response by host and therefore INF-β might be very effective in activating antivirus response.

Palliative/symptomatic treatments

An extensive literature review suggests that the majority of the patients that progress to severe form of the disease have sepsis-like symptoms with coagulopathy and multiple organ dysfunction (Wang et al., 2020; Zhou et al., 2020). Therefore, it is logical to think if palliative therapy used in sepsis could be used in COVID-19 patients. Interestingly, plasminogen inhalation therapy (that targets the clotting system) did show dramatic improvement of respiratory function in a small set of patients (Wang et al., 2020). Interestingly, inhibitors of blood clotting are also used to treat sepsis patients in clinics. Recent study using dexamethasone, a good old synthetic long acting corticosteroid ("Dexamethasone in Hospitalized Patients with Covid-19 — Preliminary Report," 2020) and reports of Tocilizumab (IL6 inhibitor) for treating COVID-19 complications, suggest a dysfunctional immune system being the cause of many complications. Likewise, given the fact that exosomes play a critical role in sepsis pathology (Essandoh et al., 2015; Raeven et al., 2018) and SARS-CoV-2 infection (Song et al., 2020), drugs targeting exosome pathways should be investigated in preclinical models. Interestingly, several drugs that target exosomes have been investigated for cancer and other diseases (reviewed in detail by Catalano & O'Driscoll (Catalano & O'Driscoll, 2020), summarized in Table 5), therefore should be investigated in pre-clinical studies to evaluate their efficacy as well as safety. In addition, mesenchymal stem cell-derived exosomes could also be used for therapeutic purposes in COVID-19 infection due to their immunomodulatory, anti-inflammatory, and regenerative properties (reviewed elsewhere in detail [(Akbari & Rezaie, 2020; Pinky et al., 2020)]. We also suggest the investigation of ceramide synthesis inhibitors in pre-clinical studies since exosome synthesis inhibitor targets this pathway (Essandoh et al., 2015). Also, ceramides have been known to activate inflammatory pathways in several metabolic and cardiovascular diseases (Bikman & Summers, 2011; Summers, 2018) that are known to have worse outcomes in COVID-19. Therefore, targeting this pathway might have a synergistic effect in controlling sepsis, inflammation, and virus dissemination through circulation. Interestingly, Opaganib, a sphingosine kinase-2 inhibitor is undergoing clinical trials for treating pneumonia caused by SARS-CoV-2 (NCT04467840).

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Abbreviations

COVID-19	Coronavirus Disease 2019
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SARS	Sever Acute Respiratory Syndrome

ACE2	Angiotensin-converting Enzyme 2
RNA	Ribonucleic Acid
CDC	Center for Disease Control
NIH	National Institute of Health
MHC	Major Histocompatibility Complex
HLA	Human Leucocyte Antigen

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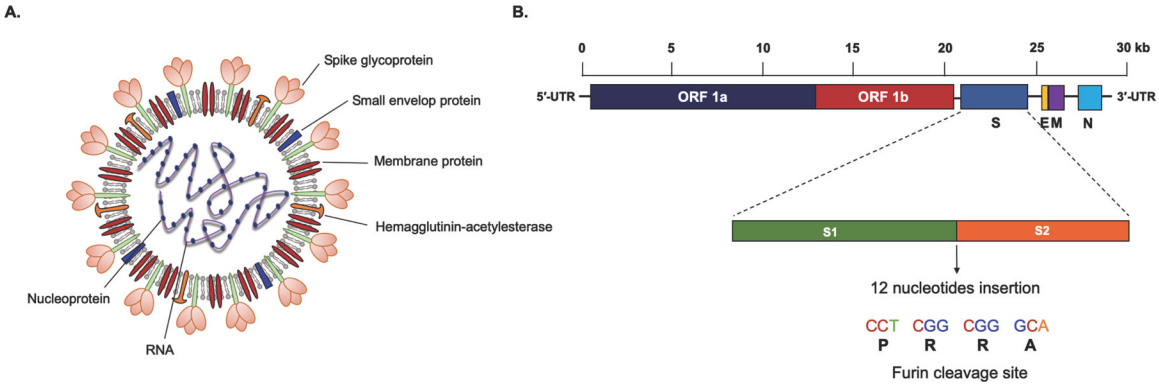

Figure 1. SARS-CoV-2 Virus

Structure and genomic organization of SARS-CoV-2. (A) A SARS-CoV-2 particle comprises of spike glycoprotein (S), small envelop protein (E), and membrane glycoprotein (M) embedded in a lipid bilayer that encloses a single-stranded RNA genome and nucleocapsid protein (N). **(B)** SARS-CoV-2 genome is a positive-sense single-stranded RNA of approximately 30 kb size. The viral genome consists of 5′-untranslated region (5′-UTR) at the N-terminal, ORF 1a and ORF 1b encoding for non-structural proteins, structural proteins include spike (S), envelop (E), membrane (M), and nucleocapsid (N), as well as 3′-UTR at the C-terminal. Expanded view of spike protein shows S1 and S2 subunits with a 12-nucleotides insertion at S1-S2 junction, which is targeted by host furins/ transmembrane proteases.

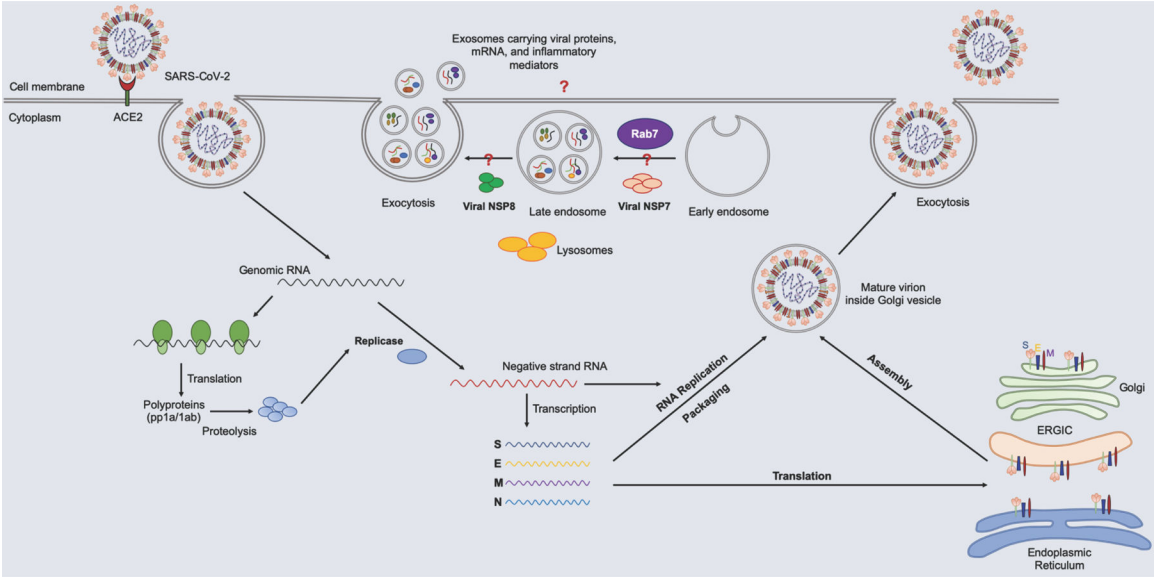

Figure 2. SARS-CoV-2 Replication

Lifecycle of SARS-CoV-2. SARS-CoV-2 enters cells via the interaction of spike protein with ACE2 present on the surface of cells. Once inside the cells, it releases its genomic RNA into the cytoplasm. The viral genome uses the host machinery to translate into polyproteins that are further proteolyzed into smaller proteins by viral proteinases. Discontinuous transcription of the positive-strand RNA results in the synthesis of subgenomic negative-strand RNA, which is translated into viral structural proteins and serves as a template for the replication of genomic RNA. Genomic RNA and nucleocapsid protein together form a nucleoprotein complex in the cytoplasm and assembled with other structural proteins, such as spike (S), envelop (E), and, membrane (M) proteins into the ER-Golgi intermediated compartment (ERGIC). New virus particles are released through exocytosis. Link between viral non-structural proteins and the Rab pathway may lead to exosome-mediated dissemination of the viral modulators, inflammatory mediators which needs to be explored.

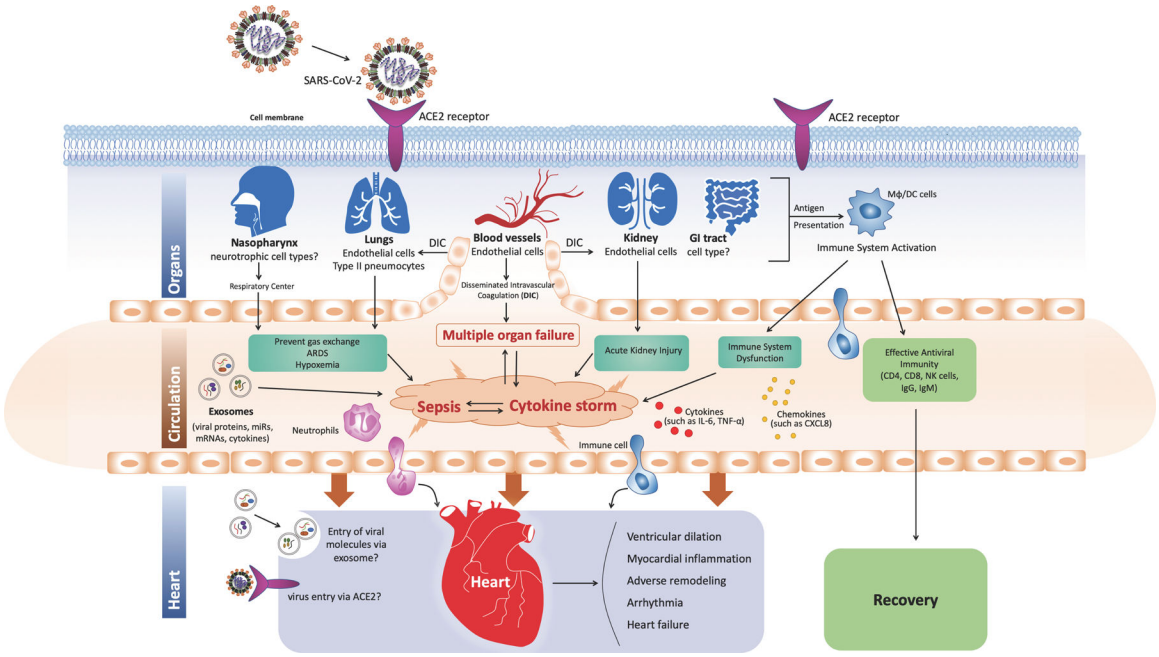

Figure 3. SARS-CoV-2 Pathogenesis

Mechanism of SARS-CoV-2-induced cardiovascular disease, role of sepsis, and exosomes. SARS-CoV-2 is capable of infecting multiple organs due to the widespread expression of ACE2 receptors. During viral replication inside cells, the immune system is activated through MHC class I antigen presentation, which is followed by effective antiviral immunity leading to recovery. However, in certain individuals, immune dysregulation results in cytokine storm and dissemination of virus in the body that might lead to sepsis. The virus can also infect endothelial cells that line the blood vessels leading to endothelialitis and disseminated intravascular coagulation, which limits gas exchange in the lungs and causes metabolic acidosis. Sepsis caused by cytokine storm, virus, exosomes, hypoxemia, and disseminated intravascular coagulation may lead to multiple-organ failure and death.

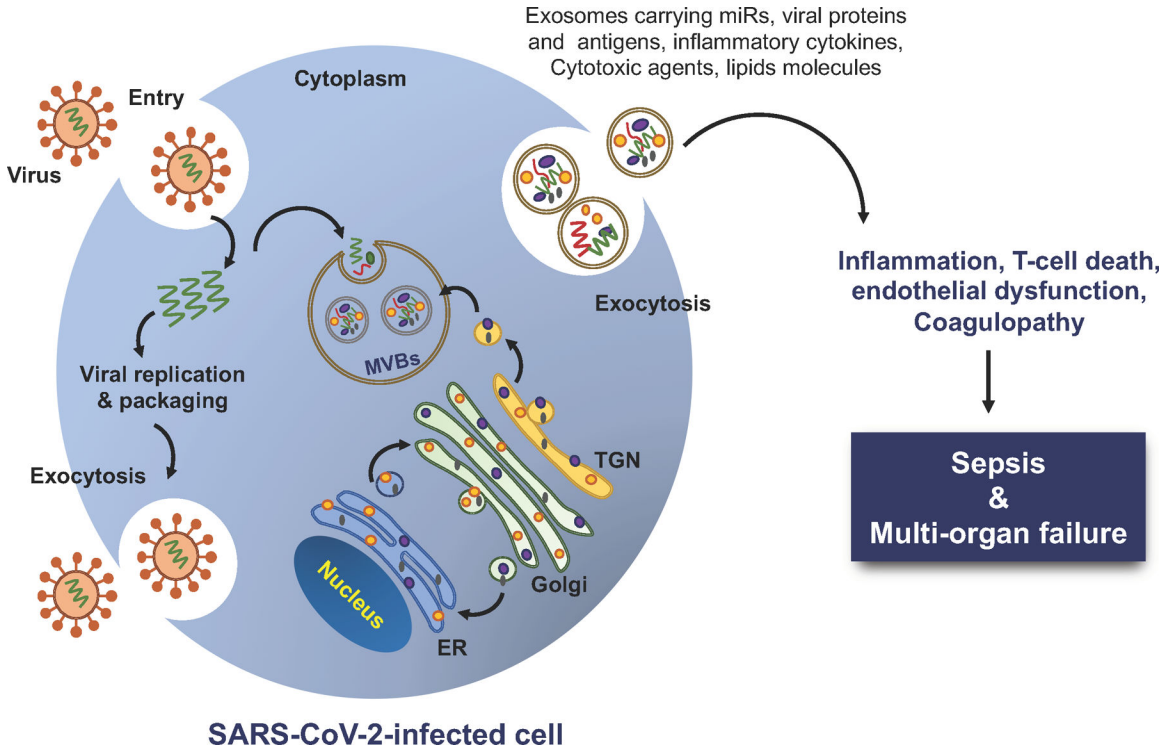

Figure 4. Hypothesized Role of Exosomes in SARS-CoV-2 Pathogenesis

Exosomes derived from virus-infected cells promote sepsis and tissue injury. Exosomes from virus-infected cells are packaged with bioactive molecules, including miRs, viral proteins, inflammatory cytokines, cytotoxic agents, and lipids that incite inflammation, activate endothelium, and affect intravascular coagulation leading to sepsis-like condition.

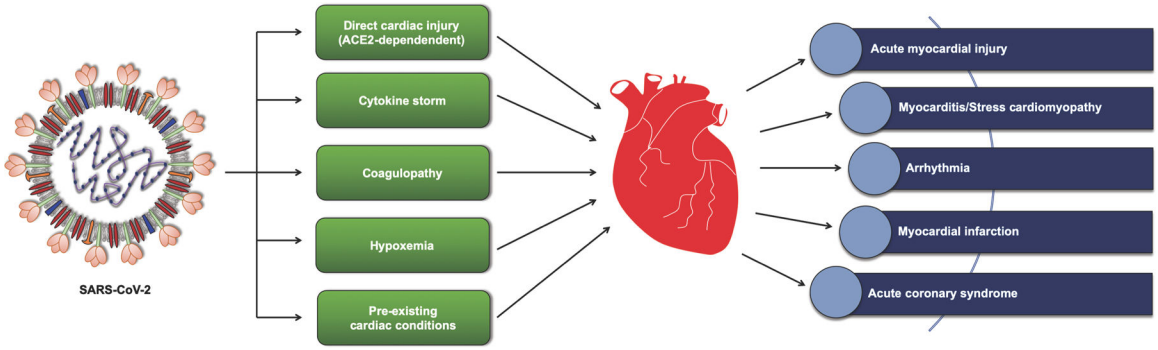

Figure 5. COVID-19 and Heart

Association between SARS-CoV-2 and heart pathophysiology. SARS-CoV-2 could affect cardiac physiology either directly via its interaction with ACE2 receptors or through other indirect mechanisms, including immune response, vascular coagulation, and oxygen deprivation. SARS-CoV-2 infection has been associated with cardiogenic shock, dysrhythmias, viral myocarditis, and acute myocardial injuries, leading to cardiac damage and fatal outcomes.

Table 1:

Organs affected, and clinical pathology associated with SARS-CoV-2

Organ/System	Symptoms	Pathological changes/Lesions	References
Respiratory tract	Dry cough, sneezing, dyspnea, Shortness of breath	Interstitial pneumonia with infiltration of immune cells, hypoxemia, metabolic acidosis	(Li et al., 2020; Zhou et al., 2020)
Gastrointestinal tract	Diarrhea	Dehydration	(Song et al., 2020)
Immune system	Fewer, viral sepsis	Lymph node atrophy, lymphopenia, cytokine storm	(Tan et al., 2020)
Heart	Rapid heart rate, fatigue, cardiac arrest	Cardiac dilatation, heart failure, Myocardial infarcts	(Libby, 2020)
Blood vessels	Rashes on foot	Microcirculation dysfunction, Inflamed blood vessels	(Varga et al., 2020)
Kidney	Blood in urine	Acute kidney injury, focal hemorrhages	(Batlle et al., 2020)
Liver		Increased ALT and AST, liver enlargement, infiltration of immune cells	(Zhang et al., 2020; Zhou et al., 2020)
Nervous system	Loss of taste and smell, Dizziness, headache	Edema and scattered degeneration	(Xydakis et al., 2020)
Blood clotting system	Increased blood clotting	Coagulopathy, deep vein thrombosis, stroke, D-Dimer	(Varga et al., 2020; Wang et al., 2020)

Table 2:

Exosomes in virus infection pathogenesis

Virus	Exosome component	Functions	References
HIV	Nef	Susceptibility to infection, Apoptosis of CD4 cells	(Arenaccio et al., 2015; Lenassi et al., 2010)
HIV	CD81	Virus budding and spread, cholesterol metabolism	(Arenaccio et al., 2015; Grigorov et al., 2009)
HIV	C19MC miRNA	Resistance to virus infection	(Delorme-Axford et al., 2013)
HIV	HIF1α-lncRNA BACE-1AS long non-coding RNA	Neuropathogenesis	(Sil et al., 2020)
Zika virus	Viral RNA and protein	Virus spread to neighboring cells	(Zhou et al., 2019)
Zika virus	unknown	Endothelialitis and blood clots	(Martínez-Rojas et al., 2020)
EV-A71 (hand-foot-and-mouth disease)	Viral protein and nucleic acid	Virus spread	(Huang et al., 2020)
Rabies Virus	unknown	Virus spread	(Wang et al., 2019)
EBV	LMP1	Inhibit cytotoxic T cells Transformation of cells	(Dukers et al., 2000)
EBV	miRNA	Virus latency	(Cai et al., 2006)
KSHV	miRNA and others	IL6 production, cellular metabolism	(Chugh et al., 2013; Meckes et al., 2013)
HSV1	HLA-DR	Immune Evasion	(Temme et al., 2010)
HCV	Viral genome	Virus spread to neighboring cells	(Ramakrishnaiah et al., 2013b)
HTLV-1	Tax protein	IL6, TNFα production and immune cell recognition	(Jaworski et al., 2014)
Avian Influenza (H5N1)	miR-483–3P	Increased production of proinflammatory cytokines in vascular endothelial cells	(Maemura et al., 2020)

Table 3:

Cardiovascular complications associated with SARS-CoV-2 infection

Pathological manifestation	Features	References
Acute myocardial injury	Elevated Troponin I and NT-proBNP levels	(Wang et al., 2020)
Cardiac Arrhythmia	Sinus tachycardia, malignant and atrial arrhythmia, Hypokalemia	(Goyal et al., 2020; Guo et al., 2020; D. Wang et al., 2020)
Viral cardiomyopathy	Cytokine storm, fulminant myocarditis	(Hu et al., 2020; Hua et al., 2020)
Myocardial infarction	Myocardial ischemia, imbalance between oxygen demand and supply, hypotension, ST-segment elevation	(Bangalore et al., 2020; Inciardi et al., 2020; Zhou et al., 2020)
Cardiogenic shock	Cardiorespiratory arrest, ST-segment elevation, dysrhythmias	(Sánchez-Recalde et al., 2020; Tavazzi et al., 2020)
Vascular complications	Venous thromboembolic events (VTEs), coagulopathy, elevated D-dimer	(Klok et al., 2020; Lodigiani et al., 2020; Tang et al., 2020; Zhou et al., 2020a)

Table 4:

Clinical trials underway to treat SARS-CoV-2 infection (source: clinicaltrials.org and Clinical Trials Arena)

Drugs	Target/mechanism
Remdesivir	Inhibits viral RNA synthesis
Danoprevir + Ritonavir	Protease inhibitor, Antiretroviral
Lopinavir + Ritonavir	Protease inhibitor
Hydroxychloroquine	Inhibits lysosomal activity (Discontinued)
Telmisartan	Angiotensin receptor blocker
Rintatolimod	Recombinant Interferon Alfa-2B
Meplazumab	Mab against CD147 membrane glycoprotein
Favipiravir	RNA dependent RNA polymerase
Galidesivir	Inhibits viral RNA synthesis
Nitazoxanide	Interfere with pyruvate:ferredoxin oxidoreductase
ACE inhibitors/ARB	Angiotensin-converting enzyme inhibitor, Angiotensin receptor blockers
Convalescent serum	Virus-neutralizing antibodies
Monoclonal antibodies to SARS-CoV-2	Virus-neutralizing antibodies
Baricitinib	Janus Kinase inhibitor
Mesenchymal stem cells	Cell therapy
Famotidine	H2 blocker
Interferon β−1b	Antiviral immune response
Peginterferon lambda alfa-1a	Antiviral immune response
SARS-CoV-2-specific T-cells	Cytotoxic T-cells
NT-17	Recombinant IL-17
Isotretinoin	Papain-like protease inhibitor
MK-4482	Antiviral
TXA127	Angiotensin 1–7
Clevudine	Pyrimidine analogue for HBV treatment
Opaganib	Sphingosine kinase-2 inhibitor

Table 5:

Exosome inhibitors that are investigated for therapy in different diseases

Pharmacological inhibitors	Target/mechanism of action	Effects
Calpeptin	Calpains/ Inhibition of MVs/EVs release	Increased anti-cancer drug susceptibility in cancer cell lines
Manumycin A	RAS GTPase/ Inhibition of EVs release	Anti-cancer activity, Increased wound healing
Y27632	ROCK1 and ROCK2/ Inhibition of production and release of MVs	Endothelial cell dysfunction
Pantethine	Cholesterol synthesis/ inhibition of MVs formation and shedding	Anti-cancer effects, anti-sclerosis, decreased severity of cerebral malaria
Imipramine	Acid sphingomyelinase/ Inhibition of MVs and EVs generation	Inhibits osteoclast differentiation and bone loss, increased efficiency of cancer chemotherapy
GW4869	Membrane neutral sphingomyelinase/ Inhibition of EVs production and release	Inhibited hypertrophic effect of cardiac fibroblasts, reduced drug-resistance in cancer cells, immune regulation
U0126	MEK 1 and MEK 2/ Inhibition of MVs generation	Inhibits coagulant activity of monocytes and macrophages
NSC23766	Rac1 GTPase/ Inhibition of MVs generation and release	Reduced MVs release from platelets in pre-clinical model of sepsis
Dimethyl amiloride (DMA)	Na^+/Ca^{2+} channels/ Inhibition of EVs release	Increased efficiency of anti-tumor drugs
Sulfisoxazole	RABs and ESCRT pathway/ Inhibition of MVs release	Anti-bacterial and anti-cancer activity