Multi-organ failure in COVID-19 patients: A possible mechanistic approach

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Abstract

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a novel single-stranded RNA virus and induces cytokines storm that play a crucial role in the pathogenetic mechanisms of acute respiratory distress syndrome and the subsequent multi-organ failure. SARS-CoV-2 enters the host cell through angiotensin-converting enzyme 2 (ACE 2) receptor and patients with forgoing chronic diseases are most vulnerable to SARS-CoV-2 infection and increase the mortality. ACE 2 is part of the renin-aldosterone angiotensin system (RAAS) which is highly expressed in the intestine, pancreas, kidney, heart, lungs, liver, maternal-fetal interface and fetal tissues. RAAS system is dysregulated in patients underlying hypertension, cardiovascular diseases, diabetes, renal disorder and preeclampsia. Drugs acting on the RAAS system, thiazolidinediones and smoking, preeclampsia, chronic liver diseases up-regulates the ACE 2 expression that may act as an entry point for SARS-CoV-2 and leading to multi-organ failure with a massive release of cytokines. Hence, this review shed a light on a path of increased mortality rate among COVID-19 patients and the possible mechanism of multi-organ failure.

Introduction

Coronavirus disease 2019 (COVID-19) is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) which is a novel single-stranded RNA virus that causes pneumonia and was first reported in Wuhan, China. Now, COVID-19 is an unprecedented challenge for the healthcare community and the World Health Organization has declared it as a global emergency on March 11, 2020 (Valencia, 2020). SARS-CoV-2 outbursts originated via zoonotic transmission related to the seafood market and later known to the person to person transmission that leads to the spreading of disease worldwide (Rothan & Byrareddy, 2020). The most common symptoms include lower respiratory tract infection, fever, dry cough, breathing problem, headache, vomiting and diarrhea (Huang et al., 2020; Jin et al., 2020). The symptoms of COVID-19 disease appears at around 5.1 days of median incubation period but in the 99% cases, the period from the beginning of COVID-19 signs to demise fluctuated from 6 to 41 days with a median of 14 days. However, this incubation period may differ from individual to individual due to the age of the patients and immune status; older the age shorter would be incubation period (Lauer et al., 2020; Rothan & Byrareddy, 2020). Epidemiological evidence reveals that mortality rates and hospitalization cases are higher among the older COVID-19 patients (Yuki, Fujiogi & Koutsogiannaki, 2020). There is a similarity in the symptoms of COVID-19 and other betacoronavirus such as severe acute respiratory syndrome (SARS) and the Middle East respiratory syndrome (MERS). However, COVID-19 present other clinical features that it specifically targets lower respiratory tract; more intense gastrointestinal symptoms such as diarrhea; and chest radiograph shows infiltration in the upper lobe of the left lung which causes dyspnea (Assiri et al., 2013; Phan et al., 2020). Reports also showed that COVID-19 patients are asymptomatic and not presenting any clinical features (Bai et al., 2020; Hu et al.,

2020). SARS-CoV-2 infection induces a two-phase immune response, the first phase of immune response is protective and seen during the incubation period in which adaptive immune response tries to eradicate the virus and prevents the disease progression at sever stages. The second phase is initiated when the first phase of immune response gets weakened and induces activation of pro-inflammatory macrophages, increased leucocytes, massive release of cytokines and ultimately leading to lung injury (Shi, Wang & Shao, 2020). Further, COVID-19 does not only infect lungs, but it also affects other vital organs where angiotensin-converting enzyme 2 (ACE 2) is highly expressed and may facilitate the virus penetration that ultimately leads to organ failure with heavy viral load and cytokine storm. Hence, this review will shed a light on a path of increased co-morbidity and mortality rate in COVID-19 patients with possible mechanism of multi-organ failure.

ACE 2, cytokines and co-morbidity in COVID-19 disease

The genome sequence analysis of human pathogenic SARS-CoV-2 is 80% identical to SARS-CoV and enter the host cell through lungs angiotensin-converting enzyme 2 (ACE 2) receptor and triggers a strong immune response which leads to a cytokine storm, generates an inflammatory response, damage the pulmonary tissue thereby induces acute respiratory distress syndrome (ARDS) (Li, Liu, Yu, Tang & Tang, 2020). Evidences showed that cytokines storm play an essential role in the pathogenetic mechanisms of multi-organ failure (Aikawa, 1996; Ura, Hirata, Yamaguchi, Katsuramaki & Denno, 1998; Wang & Ma, 2008). The overproduction of pro-inflammatory cytokines results in systemic inflammation, activation of transcription factor NF-kappaB that regulates expression of various pro-inflammatory genes and downregulates the cell-mediated immunity which impairs the balance between T helper 1 and T helper 2 cytokines and induces multi-organ damage (Ura, Hirata, Yamaguchi, Katsuramaki & Denno, 1998). Further, cytokines directly bind to the transmembrane tyrosine kinase receptor which does not have intrinsic activity and this induces dimerization of the receptor, activates the Janus kinase (JAK) and signal transducer-activator of transcription (STAT) signalling pathway thereby modulating the inflammatory and immune response (Ivashkiv, 2000; Kong, Horiguchi, Mori & Gao, 2012). Likewise, SARS-CoV-2 after interacting with ACE 2 induces the massive production of pro-inflammatory cytokines leading to cytokine storm and can increase the risk of multi-organ failure (Jose & Manuel, 2020).

The reason for multi-organ damage by SARS-CoV-2 infection in co-morbid condition is the profuse presence of ACE 2 on the intestine, heart, kidney, liver, pancreas, cerebral neurons, vascular endothelial cells, testes, immune cells, uterus, placenta and fetus (Hamming, Timens, Bulthuis, Lely, Navis & van Goor, 2004a; Roca-Ho, Riera, Palau, Pascual & Soler, 2017). Evidence is very alarming that there is an increased mortality rate in older COVID-19 patients with preexisting diseases such as hypertension which is the most common reason for the comorbidity, followed by other cardiovascular diseases, diabetes, chronic kidney disease, cerebrovascular disease, chronic obstructive pulmonary disease and lastly cancer (Hussain, Bhowmik & do Vale Moreira, 2020; Valencia, 2020). A gender-wise comparison shows that most of the COVID-19 patients were older males. Low incidences of SARS-CoV-2 infection in females might be explained by the presence of a high level of the protective hormone estrogen and progesterone, however, the exact reason is not clear (Chen et al., 2020b; Hanff, Harhay, Brown, Cohen & Mohareb, 2020). Further, patients with diabetes are often suffering from coronary artery disease, high blood pressure, coagulant-anticoagulant imbalance, renal disorder and co-existence of multiple diseases compromise the immune function and this may be another reason for the increased incidence of SARS-CoV-2 infection (Ferlita et al., 2019; Sardu, De Lucia, Wallner & Santulli, 2019). Some evidence shows that increased incidence of transmission of infectious diseases such as H1N1, influenza, staphylococcus and tuberculosis in patients with diabetes mellitus may be due to altered immune functions (Casqueiro, Casqueiro & Alves, 2012; Klekotka, Mizgała & Król, 2015). Moreover, SARS-CoV interacts with pancreatic ACE 2, damages the islet and this may lead to altered insulin secretion (Yang, Lin, Ji & Guo, 2010). In addition, diabetes, hypertension, smoking, aging and preeclampsia upregulates the ACE 2 expression which is a pivotal interacting site for SARS-CoV-2 (Leung et al., 2020; Levy, Yagil, Bursztyn, Barkalifa, Scharf & Yagil, 2008; Roca-Ho, Riera, Palau, Pascual & Soler, 2017).

Mechanism of SARS-CoV-2 transmission

Renin aldosterone-angiotensin system (RAAS), ACE 2 and COVID-19

RAAS plays a pivotal role in the liver, heart, lungs, kidney and reported to be dysregulated in hypertension, diabetes, chronic kidney diseases and other cardiovascular diseases (Petrie, Guzik & Touyz, 2018). RAAS alteration increases the production of Angiotensin II (Ang II), which induces vasoconstriction, inflammation, oxidative stress, hypertrophy and to counteract this there is a compensatory increase in the expression of 2 (Nehme, Zouein, Zayeri & Zibara, 2019; Singh, Gupta & Misra, 2020). As explained, SARS-CoV-2 enters the host cell through lung epithelial 2 receptor at low cytosolic pH which causes ARDS, lung infection and hypoxia in turn induces a massive release of cytokines, increases oxidative stress, alters myocardial oxygen demand-supply leading to myocardial injury (Cure & Cumhur Cure, 2020). Further, due to extensive lung injury by SARS-CoV-2, it may release into the blood circulation and invaded the other cells, tissue or organs where 2 is abundantly present (Heart, Kidney, Liver, Pancreas, Brain and fetus) which might provide a possible route for the entry of the SARS-CoV-2 and may induce septic shock and multi-organ failure with cytokine storms (Bornstein et al., 2020; Wang et al., 2020b).

A widely used drugs like angiotensin-converting enzyme inhibitors, angiotensin 1 receptor blockers, non-steroidal anti-inflammatory drugs and thiazolidinediones up-regulate the 2 expression thereby it may facilitate the virus transmission in kidney, heart, aorta, pancreas and liver, which might be responsible for increased co-morbidity and mortality (Leung et al., 2020; Singh, Gupta & Misra, 2020). Hence, the usage of these drugs needs to be carefully monitored among COVID-19 patients suffering from high blood pressure, other cardiovascular diseases, nephropathy and inflammatory disorders. Further, smoking may be another reason for increased mortality in the COVID-19 patients; smokers are more prone to viral respiratory tract infections as chronic exposure of cigarette smoke causes destruction of immune cells, activation of airway macrophages, increases inflammation and oxidative stress in the lungs (Feldman & Anderson, 2013). In addition, evidence reveals that smoking upregulates the ACE 2 expression in airway epithelium, alveolar macrophages and type 2 pneumocytes where the primary viral replication occurs and making patients prone to COVID-19 disease. Similarly, ACE 2 is found to be upregulated in chronic obstructive pulmonary disorder (COPD) patients, which further can amplify the SARS-CoV-2 infection and responsible for increased co-morbidity (Brake, Barnsley, Lu, McAlinden, Eapen & Sohal, 2020; Cai, Bossé, Xiao, Kheradmand & Amos, 2020). Hence, the ACE 2 upregulation by drugs, chronic smoking and COPD patients might be at higher risk of COVID-19 and may increase the mortality. Conversely, SARS-CoV-2 downregulates the lung 2 to produce a toxic level of Ang II that accumulates in the lungs which induces inflammation, fibrosis, increases oxidative stress, hypoxia and ultimately respiratory failure (Hanff, Harhay, Brown, Cohen & Mohareb, 2020).

Old age, diabetes, immune system and COVID-19

A significant deaths have been reported in comorbid condition particularly in old age patients with metabolic disease and its complications such as hypertension because this creates a low cytosolic pH condition, which is a favorable state for SARS-CoV-2 virus for binding to its ACE 2 receptor and enhances the virus transmission (Arachchillage & Laffan, 2020). Further, diabetes is associated with low-grade inflammation with systemic release of cytokines, thrombotic events and this can lead to rapid deterioration of patients of COVID-19 due to the additive burden of cytokine storm and may increase the mortality in co-morbidity (Randeria, Thomson, Nell, Roberts & Pretorius, 2019). There is global diversity in severity and mortality among COVID-19 patients because of the diverse ethnic, geographical and immune system of patients. The immune system is one of the major contributing factors for increased mortality rate in COVID-19 patients because there is a suppression of the immune system due to chronic diabetes, cancer, immunosuppressant therapy, corticosteroids and aging which making patients more prone towards SARS-CoV-2 infection and may increase the co-morbidity and mortality rate (Bornstein et al., 2020; Ferlita et al., 2019).

Neuronal, gastrointestinal, hepatic system and COVID-19

COVID-19 leads to lung injury, ARDS, and respiratory failure. The respiration is mainly regulated by the respiratory center, which is located in the medulla oblongata and pons, in the brain stem (Ikeda et al., 2017). Reports show that Middle East Respiratory Syndrome Coronavirus (MERS-CoV) and SARS-

CoV infect the brain stem leading to neurological complications (Algahtani, Subahi & Shirah, 2016; Arabi et al., 2015; Hwang, 2006; McCray et al., 2007; Tsai et al., 2004). Growing evidence shows that patients infected with SARS-CoV-2 present neurological symptoms like headache, nausea, vomiting, cerebrovascular disease, skeletal muscle injury and impaired consciousness (Li, Bai & Hashikawa, 2020; Mao et al., 2020). The consciousness is regulated by the reticular activating system via activation of the cerebral cortex and here arises a question that could SARS-CoV-2 alter the reticular activating system and as well, brain stem function. Aforementioned, SARS-COV-2 induces lung injury, alters RAAS system in the pneumocytes which leads to the production of cytokines and cytokine storm has been observed in patients underlying with pre-existing diseases such as diabetes, myocardial injury. Yarlagadda et al. reported that cytokines can cross the blood-brain barrier and cause significant brain damage (Yarlagadda, Alfson & Clayton, 2009). Further, circulating cytokines alters the hypothalamus function which regulates body temperature and causes high fever; a common symptom in COVID-19 patients (Netea, Kullberg & Van der Meer, 2000). Xia et al. reported that neuronal ACE 2 plays an important role in the compensatory regulation of neurogenic hypertension in mice due to dysregulated RAAS (Feng et al., 2010). Hence, if SARS-CoV-2 crosses the blood-brain barrier then it might interact with neuronal ACE 2 which can affect the brain functions and capable enough to induce fatal neurological changes. Further fever, pneumonia is a common symptom among COVID-19 disease but patients are also reporting with gastrointestinal issues like abdominal pain, anorexia, vomiting and diarrhea (Pan et al., 2020; Song et al., 2020; Wong & Lui, 2020; Zhang et al., 2020a). Wang et al. reported that respiratory influenza virus infection induces injury in intestine cells, altered the intestinal microbiota composition, enhances the production of the pro-inflammatory cytokine, altered immune cells functions and induces Th17 cell-dependent inflammation (Wang, Li, Wei, Lian, Sun & Tian, 2014). Hamming et al. reported that ACE 2 is most profusely present in the epithelial cells of the intestine, duodenum, jejunum and ileum which is a pivotal entry point of SARS-CoV-2 and may infect the intestinal cells, alter the functioning of immune cells, imbalance the microbiota composition, impaired the intestinal function and causes diarrhea (Hamming, Timens, Bulthuis, Lely, Navis & van Goor, 2004b). Further, several reports are advocating that detection of SARS-CoV-2 in the stools samples of COVID-19 patients which may strengthen the fact that invasion of the virus to the intestine and incidence of diarrhea. Hence, there would be chances of virus transmission through the fecal-oral route (Wang et al., 2020a; Wu et al., 2020; Zhang et al., 2020b).

Non-alcoholic steatohepatitis (NASH), which is characterized by liver cell injury with high levels of pro-inflammatory cytokines that makes COVID-19 patients more prone to additive cytokine burden leading to severe liver damage that amplify the risk for liver fibrosis and carcinogenesis (Syn, Choi & Diehl, 2009). Further, patients with non-alcoholic fatty liver diseases (NAFLD) and NASH have impaired intestinal permeability with a disrupted tight junction in the intestine, altered gut microbiota, increased production of endotoxins (Lau, Carvalho & Freitas, 2015; Takaki, Kawai & Yamamoto, 2013). Lau et al. reported that liver received about 70% of blood supply from the intestine and this enhance the endotoxin translocation from gut to the liver, which in turn to activates toll-like receptors which further promotes inflammation and fibrosis in the liver (Lau, Carvalho & Freitas, 2015). Further, there is evidence of SARS-CoV-2 infection in the intestine and is presence in faecal samples. Therefore, due to impaired permeability of intestinal tight junction virus may invade the hepatic tissue and may further aggravate the cytokine release in NASH patients. Moreover, reports show that ACE 2 is expressed in the epithelial cells of the bile duct and hepatic tissue with lower abundance but the chronic liver injury upregulates the hepatic ACE 2 expression which is a key entry point for SARS-CoV-2 (Huang et al., 2009; Paizis et al., 2005). Hence, NAFLD and NASH patients with the high level of cytokines are more prone to the cytokine storm and this may induce irreversible damage of hepatic tissue and at later stage liver transplantation can only be viable option. Further, careful monitoring is needed among patients on the drugs that have a potential to upregulates the ACE 2.

Pregnancy and COVID-19

Preeclampsia is a pregnancy complication characterized as hypertension, proteinuria and usually begins after 20 weeks gestation period which is a major cause of maternal deaths and fetal morbidity and mortality and Lumbers et al. reported that the RAAS system undergoes major changes during preeclampsia (Lumbers & Pringle, 2014). Levels of Ang II and aldosterone increase after 20 weeks of gestation in women that causes

preeclampsia. To counteract this, there is compensatory up-regulation of 2 to produce Ang (1-7), a vasodilator and reduces the aldosterone production (Bharadwaj et al., 2011; Levy, Yagil, Bursztyn, Barkalifa, Scharf & Yagil, 2008). The reports on Zika, H1N1 and SARS-CoV infection during pregnancy linked these infections with preterm birth, maternal death and abortions (Ksiezakowska, Laszczyk, Wilczyński & Nowakowska, 2008; Rasmussen, Smulian, Lednicky, Wen & Jamieson, 2020). Till now, the implications of maternal SARS-CoV-2 infection on the fetal health are unknown, however. reports shows that during pregnancy and preeclampsia 2 is highly expressed in the placenta, maternal-fetal interface, fetal tissues such as liver, heart, and lung which may facilitate the SARS-CoV-2 transmission from infected mother to fetus which may increase the risk to neonates (Levy, Yagil, Bursztyn, Barkalifa, Scharf & Yagil, 2008; Li, Chen, Zhang, Xiong & Li, 2020; Yang, Shang, Zhang, Li & Liu, 2013). Reports also showed that pregnant females infected with virus experienced decreased fetal movement, anemia, dyspnea, intrauterine growth restriction and newborn is infected with SARS-CoV-2 (Chen et al., 2020a; Dashraath et al., 2020; Di Mascio et al., 2020). Hence, there is a reason for the worry as SARS-CoV-2 might interact with highly expressed ACE 2 in pregnancy and may be responsible for fetal morbidity and mortality.

Conclusion

We are hypothesizing that the profuse presence of ACE 2 and its upregulation in different pathological conditions making patients more susceptible to SARS-CoV-2 infection and can contribute to an increase in co-morbidity and mortality. COVID-19 is a global concern and its pathophysiology is very complex which creating an illusion towards the use of first-line drugs in the treatments of preeclampsia, cardiovascular diseases, diabetes and its complications, asthma, NASH, immune-related diseases and cancer. Hence, there is an urgent need for care to those patients who have SARS-CoV-2 infection underlying with multiple diseases and its delay in diagnosis may increase the severity and mortality in comorbid conditions due to multi-organ transmission of infection with a heavy load of virus and cytokine storm (Figure 1). Hence targeting the interaction of SARS-CoV-2 to ACE 2 could be the future novel therapeutic approach to alleviate the multi-organ transmission and failure.

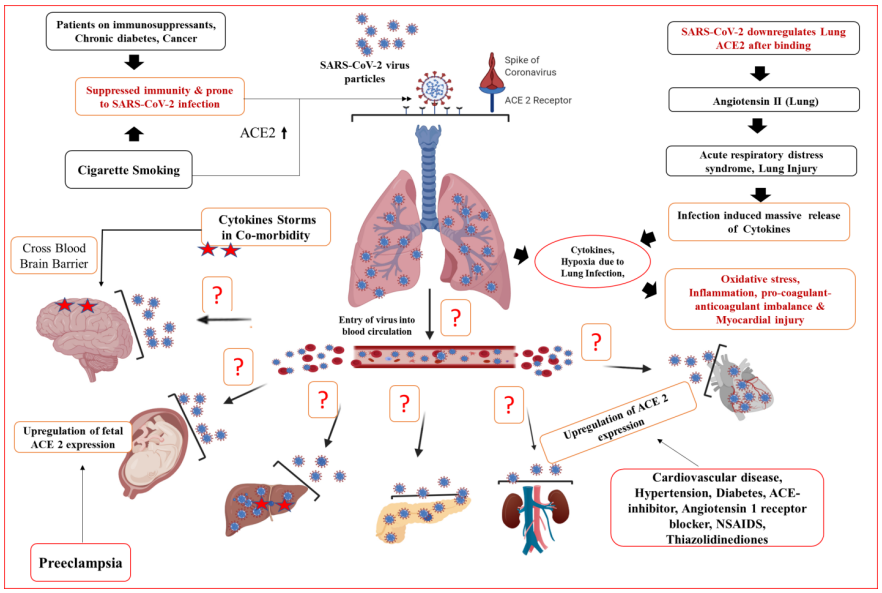

Figure 1: COVID-19 and comorbidity: Hypothetical pathways of SARS-CoV-2 infection-induced multi-organ failure.

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References

Aikawa N (1996). [Cytokine storm in the pathogenesis of multiple organ dysfunction syndrome associated with surgical insults]. Nihon Geka Gakkai zasshi 97**:** 771-777.

Algahtani H, Subahi A, & Shirah B (2016). Neurological Complications of Middle East Respiratory Syndrome Coronavirus: A Report of Two Cases and Review of the Literature. Case Rep Neurol Med 2016**:** 3502683.

Arabi YM, Harthi A, Hussein J, Bouchama A, Johani S, Hajeer AH*, et al.* (2015). Severe neurologic syndrome associated with Middle East respiratory syndrome corona virus (MERS-CoV). Infection 43**:** 495-501.

Arachchillage DRJ, & Laffan M (2020). Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. J Thromb Haemost 18**:**1233-1234.

Assiri A, Al-Tawfiq JA, Al-Rabeeah AA, Al-Rabiah FA, Al-Hajjar S, Al-Barrak A*, et al.* (2013). Epidemiological, demographic, and clinical characteristics of 47 cases of Middle East respiratory syndrome coronavirus disease from Saudi Arabia: a descriptive study. Lancet Infect Dis 13**:** 752-761.

Bai Y, Yao L, Wei T, Tian F, Jin D-Y, Chen L*, et al.* (2020). Presumed asymptomatic carrier transmission of COVID-19. Jama 323**:** 1406-1407.

Bharadwaj MS, Strawn WB, Groban L, Yamaleyeva LM, Chappell MC, Horta C*, et al.* (2011). Angiotensin-converting enzyme 2 deficiency is associated with impaired gestational weight gain and fetal growth restriction. Hypertension 58**:** 852-858.

Bornstein SR, Rubino F, Khunti K, Mingrone G, Hopkins D, Birkenfeld AL*, et al.* (2020). Practical recommendations for the management of diabetes in patients with COVID-19. Lancet Diabetes Endocrinol.

Brake SJ, Barnsley K, Lu W, McAlinden KD, Eapen MS, & Sohal SS (2020). Smoking Upregulates Angiotensin-Converting Enzyme-2 Receptor: A Potential Adhesion Site for Novel Coronavirus SARS-CoV-2 (Covid-19). J Clin Med 9.

Cai G, Bossé Y, Xiao F, Kheradmand F, & Amos CI (2020). Tobacco Smoking Increases the Lung Gene Expression of ACE2, the Receptor of SARS-CoV-2. Am J Respir Crit Care Med.

Casqueiro J, Casqueiro J, & Alves C (2012). Infections in patients with diabetes mellitus: A review of pathogenesis. Indian J Endocrinol Metab 16 Suppl 1**:** S27-36.

Chen H, Guo J, Wang C, Luo F, Yu X, Zhang W*, et al.* (2020a). Clinical characteristics and intrauterine vertical transmission potential of COVID-19 infection in nine pregnant women: a retrospective review of medical records. Lancet 395**:** 809-815.

Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y*, et al.* (2020b). Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet 395**:** 507-513.

Cure E, & Cumhur Cure M (2020). Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers may be harmful in patients with diabetes during COVID-19 pandemic. Diabetes Metab Syndr 14**:** 349-350.

Dashraath P, Jeslyn WJL, Karen LMX, Min LL, Sarah L, Biswas A*, et al.* (2020). Coronavirus disease 2019 (COVID-19) pandemic and pregnancy. Am J Obstet Gynecol.

Di Mascio D, Khalil A, Saccone G, Rizzo G, Buca D, Liberati M*, et al.* (2020). Outcome of Coronavirus spectrum infections (SARS, MERS, COVID 1 -19) during pregnancy: a systematic review and meta-analysis. Am J Obstet Gynecol MFM**:** 100107.

Feldman C, & Anderson R (2013). Cigarette smoking and mechanisms of susceptibility to infections of the respiratory tract and other organ systems. J Infect 67**:**169-184.

Feng Y, Xia H, Cai Y, Halabi CM, Becker LK, Santos RA*, et al.* (2010). Brain-selective overexpression of human Angiotensin-converting enzyme type 2 attenuates neurogenic hypertension. Circ Res 106**:** 373-382.

Ferlita S, Yegiazaryan A, Noori N, Lal G, Nguyen T, To K*, et al.* (2019). Type 2 Diabetes Mellitus and Altered Immune System Leading to Susceptibility to Pathogens, Especially Mycobacterium tuberculosis. J Clin Med 8.

Hamming I, Timens W, Bulthuis M, Lely A, Navis G, & van Goor H (2004a). Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis. J Pathol 203**:** 631-637.

Hamming I, Timens W, Bulthuis ML, Lely AT, Navis G, & van Goor H (2004b). Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis. J Pathol 203**:** 631-637.

Hanff TC, Harhay MO, Brown TS, Cohen JB, & Mohareb AM (2020). Is There an Association Between COVID-19 Mortality and the Renin-Angiotensin System-a Call for Epidemiologic Investigations. Clin Infect Dis.

Hu Z, Song C, Xu C, Jin G, Chen Y, Xu X*, et al.* (2020). Clinical characteristics of 24 asymptomatic infections with COVID-19 screened among close contacts in Nanjing, China. Sci China Life Sci 63**:** 706-711.

Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y*, et al.* (2020). Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 395**:** 497-506.

Huang Q, Xie Q, Shi C-C, Xiang X-G, Lin L-Y, Gong B-D*, et al.* (2009). Expression of angiotensin-converting enzyme 2 in CCL4-induced rat liver fibrosis. International journal of molecular medicine 23**:** 717-723.

Hussain A, Bhowmik B, & do Vale Moreira NC (2020). COVID-19 and diabetes: Knowledge in progress. Diabetes Res Clin Pract 162**:** 108142.

Hwang CS (2006). Olfactory neuropathy in severe acute respiratory syndrome: report of A case. Acta Neurol Taiwan 15**:** 26-28.

Ikeda K, Kawakami K, Onimaru H, Okada Y, Yokota S, Koshiya N*, et al.* (2017). The respiratory control mechanisms in the brainstem and spinal cord: integrative views of the neuroanatomy and neurophysiology. J Physiol Sci 67**:** 45-62.

Ivashkiv LB (2000). Jak-STAT signaling pathways in cells of the immune system. Reviews in immunogenetics 2**:** 220-230.

Jin X, Lian JS, Hu JH, Gao J, Zheng L, Zhang YM*, et al.* (2020). Epidemiological, clinical and virological characteristics of 74 cases of coronavirus-infected disease 2019 (COVID-19) with gastrointestinal symptoms. Gut 69**:**1002-1009.

Jose RJ, & Manuel A (2020). COVID-19 cytokine storm: the interplay between inflammation and coagulation. The Lancet Respiratory medicine.

Klekotka RB, Mizgała E, & Król W (2015). The etiology of lower respiratory tract infections in people with diabetes. Pneumonol Alergol Pol 83**:** 401-408.

Kong X, Horiguchi N, Mori M, & Gao B (2012). Cytokines and STATs in liver fibrosis. Frontiers in physiology 3**:** 69.

Ksiezakowska K, Laszczyk M, Wilczyński J, & Nowakowska D (2008). [SARS-CoV infection and pregnancy]. Ginekol Pol 79**:** 47-50.

Lau E, Carvalho D, & Freitas P (2015). Gut microbiota: association with NAFLD and metabolic disturbances. BioMed research international 2015.

Lauer SA, Grantz KH, Bi Q, Jones FK, Zheng Q, Meredith HR*, et al.* (2020). The Incubation Period of Coronavirus Disease 2019 (COVID-19) From Publicly Reported Confirmed Cases: Estimation and Application. Ann Intern Med 172**:** 577-582.

Leung JM, Yang CX, Tam A, Shaipanich T, Hackett TL, Singhera GK*, et al.* (2020). ACE-2 Expression in the Small Airway Epithelia of Smokers and COPD Patients: Implications for COVID-19. Eur Respir J.

Levy A, Yagil Y, Bursztyn M, Barkalifa R, Scharf S, & Yagil C (2008). ACE2 expression and activity are enhanced during pregnancy. Am J Physiol Regul Integr Comp Physiol 295**:** R1953-1961.

Li H, Liu SM, Yu XH, Tang SL, & Tang CK (2020). Coronavirus disease 2019 (COVID-19): current status and future perspectives. Int J Antimicrob Agents**:** 105951.

Li M, Chen L, Zhang J, Xiong C, & Li X (2020). The SARS-CoV-2 receptor ACE2 expression of maternal-fetal interface and fetal organs by single-cell transcriptome study. PLoS One 15**:** e0230295.

Li YC, Bai WZ, & Hashikawa T (2020). The neuroinvasive potential of SARS-CoV2 may play a role in the respiratory failure of COVID-19 patients. J Med Virol.

Lumbers ER, & Pringle KG (2014). Roles of the circulating renin-angiotensin-aldosterone system in human pregnancy. Am J Physiol Regul Integr Comp Physiol 306**:** R91-101.

Mao L, Jin H, Wang M, Hu Y, Chen S, He Q*, et al.* (2020). Neurologic Manifestations of Hospitalized Patients With Coronavirus Disease 2019 in Wuhan, China. JAMA Neurol.

McCray PB, Jr., Pewe L, Wohlford-Lenane C, Hickey M, Manzel L, Shi L*, et al.* (2007). Lethal infection of K18-hACE2 mice infected with severe acute respiratory syndrome coronavirus. J Virol 81**:** 813-821.

Nehme A, Zouein FA, Zayeri ZD, & Zibara K (2019). An Update on the Tissue Renin Angiotensin System and Its Role in Physiology and Pathology. J Cardiovasc Dev Dis 6.

Netea MG, Kullberg BJ, & Van der Meer JW (2000). Circulating cytokines as mediators of fever. Clin Infect Dis 31 Suppl 5**:** S178-184.

Paizis G, Tikellis C, Cooper ME, Schembri JM, Lew RA, Smith AI*, et al.* (2005). Chronic liver injury in rats and humans upregulates the novel enzyme angiotensin converting enzyme 2. Gut 54**:** 1790-1796.

Pan L, Mu M, Yang P, Sun Y, Wang R, Yan J*, et al.* (2020). Clinical Characteristics of COVID-19 Patients With Digestive Symptoms in Hubei, China: A Descriptive, Cross-Sectional, Multicenter Study. Am J Gastroenterol 115**:**766-773.

Petrie JR, Guzik TJ, & Touyz RM (2018). Diabetes, Hypertension, and Cardiovascular Disease: Clinical Insights and Vascular Mechanisms. Can J Cardiol 34**:** 575-584.

Phan LT, Nguyen TV, Luong QC, Nguyen TV, Nguyen HT, Le HQ*, et al.* (2020). Importation and Human-to-Human Transmission of a Novel Coronavirus in Vietnam. N Engl J Med 382**:** 872-874.

Randeria SN, Thomson GJA, Nell TA, Roberts T, & Pretorius E (2019). Inflammatory cytokines in type 2 diabetes mellitus as facilitators of hypercoagulation and abnormal clot formation. Cardiovasc Diabetol 18**:** 72.

Rasmussen SA, Smulian JC, Lednicky JA, Wen TS, & Jamieson DJ (2020). Coronavirus Disease 2019 (COVID-19) and pregnancy: what obstetricians need to know. Am J Obstet Gynecol 222**:** 415-426.

Roca-Ho H, Riera M, Palau V, Pascual J, & Soler MJ (2017). Characterization of ACE and ACE2 Expression within Different Organs of the NOD Mouse. Int J Mol Sci 18.

Rothan HA, & Byrareddy SN (2020). The epidemiology and pathogenesis of coronavirus disease (COVID-19) outbreak. J Autoimmun 109**:** 102433.

Sardu C, De Lucia C, Wallner M, & Santulli G (2019). Diabetes Mellitus and Its Cardiovascular Complications: New Insights into an Old Disease. J Diabetes Res 2019**:** 1905194.

Shi Y, Wang Y, & Shao C (2020). COVID-19 infection: the perspectives on immune responses. Cell Death Differ 27**:** 1451-1454.

Singh AK, Gupta R, & Misra A (2020). Comorbidities in COVID-19: Outcomes in hypertensive cohort and controversies with renin angiotensin system blockers. Diabetes Metab Syndr 14**:** 283-287.

Song Y, Liu P, Shi XL, Chu YL, Zhang J, Xia J*, et al.* (2020). SARS-CoV-2 induced diarrhoea as onset symptom in patient with COVID-19. Gut 69**:** 1143-1144.

Syn W-K, Choi SS, & Diehl AM (2009). Apoptosis and cytokines in non-alcoholic steatohepatitis. Clinics in liver disease 13**:** 565-580.

Takaki A, Kawai D, & Yamamoto K (2013). Multiple hits, including oxidative stress, as pathogenesis and treatment target in non-alcoholic steatohepatitis (NASH). International journal of molecular sciences 14**:** 20704-20728.

Tsai LK, Hsieh ST, Chao CC, Chen YC, Lin YH, Chang SC*, et al.* (2004). Neuromuscular disorders in severe acute respiratory syndrome. Arch Neurol 61**:** 1669-1673.

Ura H, Hirata K, Yamaguchi K, Katsuramaki T, & Denno R (1998). [Mechanism of the development of organ failure]. Nihon Geka Gakkai zasshi 99**:** 485-489.

Valencia DN (2020). Brief review on COVID-19: the 2020 pandemic caused by SARS-CoV-2. J Cureus 12.

Wang H, & Ma S (2008). The cytokine storm and factors determining the sequence and severity of organ dysfunction in multiple organ dysfunction syndrome. The American journal of emergency medicine 26**:** 711-715.

Wang J, Li F, Wei H, Lian ZX, Sun R, & Tian Z (2014). Respiratory influenza virus infection induces intestinal immune injury via microbiota-mediated Th17 cell-dependent inflammation. J Exp Med 211**:** 2397-2410.

Wang W, Xu Y, Gao R, Lu R, Han K, Wu G*, et al.* (2020a). Detection of SARS-CoV-2 in Different Types of Clinical Specimens. Jama.

Wang W, Xu Y, Gao R, Lu R, Han K, Wu G*, et al.* (2020b). Detection of SARS-CoV-2 in Different Types of Clinical Specimens. Jama.

Wong SH, & Lui RN (2020). Covid-19 and the digestive system. J Gastroenterol Hepatol 35**:** 744-748.

Wu Y, Guo C, Tang L, Hong Z, Zhou J, Dong X*, et al.* (2020). Prolonged presence of SARS-CoV-2 viral RNA in faecal samples. Lancet Gastroenterol Hepatol 5**:** 434-435.

Yang J, Shang J, Zhang S, Li H, & Liu H (2013). The role of the renin-angiotensin-aldosterone system in preeclampsia: genetic polymorphisms and microRNA. J Mol Endocrinol 50**:** R53-66.

Yang JK, Lin SS, Ji XJ, & Guo LM (2010). Binding of SARS coronavirus to its receptor damages islets and causes acute diabetes. Acta Diabetol 47**:** 193-199.

Yarlagadda A, Alfson E, & Clayton AH (2009). The blood brain barrier and the role of cytokines in neuropsychiatry. Psychiatry (Edgmont) 6**:** 18-22.

Yuki K, Fujiogi M, & Koutsogiannaki S (2020). COVID-19 pathophysiology: A review. Clin Immunol 215:108427.

Zhang H, Li HB, Lyu JR, Lei XM, Li W, Wu G, *et al.* (2020a). Specific ACE2 Expression in Small Intestinal Enterocytes may Cause Gastrointestinal Symptoms and Injury after 2019-nCoV Infection. Int J Infect Dis.

Zhang T, Cui X, Zhao X, Wang J, Zheng J, Zheng G, *et al.* (2020b). Detectable SARS-CoV-2 viral RNA in feces of three children during recovery period of COVID-19 pneumonia. J Med Virol.