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Sys Rev Pharm 2020;11(10):1252-1256
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Cytokines Storm Of COVID-19 And Multi Systemic Organ Failure: A Review

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ABSTRACT
Coronavirus disease 2019 (COVID-19), Coronavirus causes severe acute respiratory syndrome (SARS-CoV-2), and has spread around the world as a serious pandemic. The worldwide epidemic of the SARS outbreak was reported in 2002-2003 that the CFR was estimated at 9.6% globally and much lower than the CFR of 6.4% in mainland China, while the MERS outbreak had a much higher rate than the CFR. COVID-19 may present with ARDS and respiratory failure from pneumonia with or without cardiogenic shock ± distributive . In contrast, airborne transmission may happen through two dissimilar situations and need physical contact between susceptible individuals and infected.
Keywords: Cytokines Storm Of COVID-19, Multi Systemic Organ Failure, A Review
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INTRODUCTION

Coronavirus disease 2019 (COVID-19), Coronavirus causes severe acute respiratory syndrome (SARS-CoV-2), and has spread around the world as a serious pandemic [CCDC,2020]. The emerging corona virus is a virus encapsulated with a large genome of unfragmented, single-stranded RNA genome, 32 kbps insensitive [Ksiazek,2003], and is a member of the Corona viridae (CoV) family that causes mostly respiratory disease with a wide spread of a range of clinical severity, ranging from Mild asymptomatic symptoms (fever, cough, shortness of breath, muscle pain, diarrhea, and fatigue) in a great proportion of patients to multi-organ sepsis and severe acute respiratory distress syndrome (ARDS) [Huang*et al*, 2020;Wang*et al,* 2003].

The worldwide epidemic of the SARS outbreak was reported in 2002-2003 that the CFR was estimated at 9.6% globally and much lower than the CFR of 6.4% in mainland China, while the MERS outbreak had a much higher rate than the CFR. With a 34.5% global case fatality rate (CFR) 37.1% Saudi Arabia (Donnelly *et al*,2003;Lin *et al*,2018;Zhao *et al,*2020). The disease has a case fatality rate ranging from less than 0.5% to more than 7% (average, 3.8%), so Covid 19 More contagious than influenza, its high transmission rate and poor sanitation by people have led to a relatively high rate of causing serious complications, which has led to the transformation of COVID-19 into a serious threat to public health all over the world [David *et al*2020]. Among the various physiological consequences Severe COVID-19 leads to comorbidities such as cardiovascular complications, kidney failure, diffuse thrombosis and multi-organ sepsis, and these diseases have emerged as one of the most serious and life-threatening diseases [Wu, *et al*. 2020;Mehta*et al*. 2020;Zhang *et al*. 2020].

COVID-19 may present with ARDS and respiratory failure from pneumonia, with or without cardiogenic shock± distributive [Zhang, *et al*. 2020 ;Thierry*et al*. 2020]. DrTedrosAdhanomGhebreyesus, Director-General of WHO on Feb 11, 2020 and severe cardiac injury manifesting as elevated markedly troponin and heart failure [*Shi Set al,2020;*Wang D, Hu B, Hu C, *et al*(2020]. All these complication occurs as prognosis of immune defense against covid19All these complication occurs as prognosis of immune defense against covid19. [Bonow*et al*, 2020;Clerkin*et al*, 2020;Adriano]. For well understanding how Immune system play in two side first after infection by Covid19 either direct or indirect "contact" modes require a sensitive person to physically touch themselves, for example, with a hand contaminated with the virus; The word "direct" indicates that person-to-person contact transmits the virus between infected and susceptible hosts (such as a handshake), while "indirect" refers to transmission via "fomite," something like a hand penis or tissue paper contaminated with an infectious virus(Chan*et al*,2020;Duguid, 1946).

In contrast, airborne transmission may happen through two dissimilar situations and need physical contact between susceptible individuals and infected. While sneezing or coughing, "droplet sprays" from respiratory fluids carrying the virus, usually more than 5 mm in diameter, directly affect the susceptible individual. Alternatively, a sensitive person can inhale microscopic aerosol particles that consist of the solid components remaining from the vaporized respiratory droplets, which are small enough (<5 mm) to remain airborne for hours [Tellier,2019;Lindsley,2013].

It is uncertain which of these mechanisms plays a main role in the diffusion of COVID-19. Much of the airborne illnessinvestigation prior to the present pandemic focused on "violent" exhaled events such as sneezing and coughing [Bourouiba,2014].

Cytokines are small polypeptides with a wide range of inflammatory ,metabolic and immunomodulatory propertiesand tissue homeostasis[Entedhar *et al*,2019;Sarhat *et al*,2020].After passing the upper respiratory canal reach to the lung than persist in alveolar and infected the surfactant cell which contained specific receptor Angiotensin-converting enzyme 2 (ACE2) receptor which enter to the cell by endocytosis and since the virus are positive sense it translated their structural and non-structural protein that required for virus replication on by ribosome of cell. Releasing large amount of virus cause damaging alveolar cell, the immune system is activated to encounter the effect of virus also release INF (α & β)released from damaged cell that trigger the other healthy alveolar cell by stimulating them to synthetizing ant-vial peptides used to break down of the viruses also they release of damage associated molecules pattern as well as amounts of inflammatory cytokines which alert the alveolar macrophage for secreting a lot of inflammatory media (IL6, IL8, TNF, INF σ) [Wu, *et al*2020;Li *et al*,2020;Mohammed IJ*et al*,2020].

The IL6 and IL8 pass to pulmonary capillary result in leaking of fluid from capillaries formed interstitial edema some of fluid may move enter alveoli make alveolar edema effected on the movement of oxygen to blood as result formed hypoxemia, hypercapnia and Respiratory acidosis [Ware, 2006;Gattinoni,2020].. As the same time these IL6& IL8 lead to increase expression of particular protein on the endothelium cell adhesion molecule and chemokines receptors on neutrophils versus monocytes VACAM-1whic in pull the neutrophils to the alveoli (site of inflammation) also activated with the above inflammatory cytokines(IL8) [John;2010] molecular immunology).

These neutrophil worked as helpful and at the same time not formed well response because after activation by IL8 secreted elastase, proteases andreactive oxygen species (ROS) to eliminate an invading pathogen beside their ability to destroy the cause inflammation but also damage alveolar cell both surfactant cell type II and gas changing cell type I [Philippe,2019], as prognosis of damaging type I decrease of as exchange process between blood and alveolar formed hypoxemia that can potentially lead to shortness of breath within decrease of surfactant all these at the result formed decreased of surface tension and alveolar collapse [Perrier*et al*. 2019] .

These above cytokine stromata (Fig. 1) occurred in alveolar also effected directly or indirectly on increasing of pro coagulant (thrombi formation) on the other site decreased entire coagulant activity and they responsible for clot formation(pulmonary emboli) which is risky effect of virus occurred with severe case of disease [AzharHussain*et al*,2020]. In addition of above cytokines, the infected alveoli released others such as Leukotriene, prostaglandin and Bradykinin all these activated receptors that connected to vaguse nerve stimulate inflammatory generated cough reflex by CNS commonly they are dry cough may be productive cough also the bradykinin act on bronchial smooth muscle lead to bronchial construction which decreased the oxygen flowing into alveoli at the same increase of CO_2 in alveoli formed hypoxemia [Marie Eve Moreau,2020]. All the inflammatory process spread out of the alveoli called systemic inflammatory response syndromes (SIRS) resulted increase of pro coagulant within decrease of anti-coagulant in circular stream cause multiple clot in circular system with consuming of coagulant protein called Disseminated intravascular coagulation (DIC). Also the IL1 & TNα can move also to circulation act on hypothalamus lead to increase of temperature fever which is main symptom of covid 19 [Tang,2020].

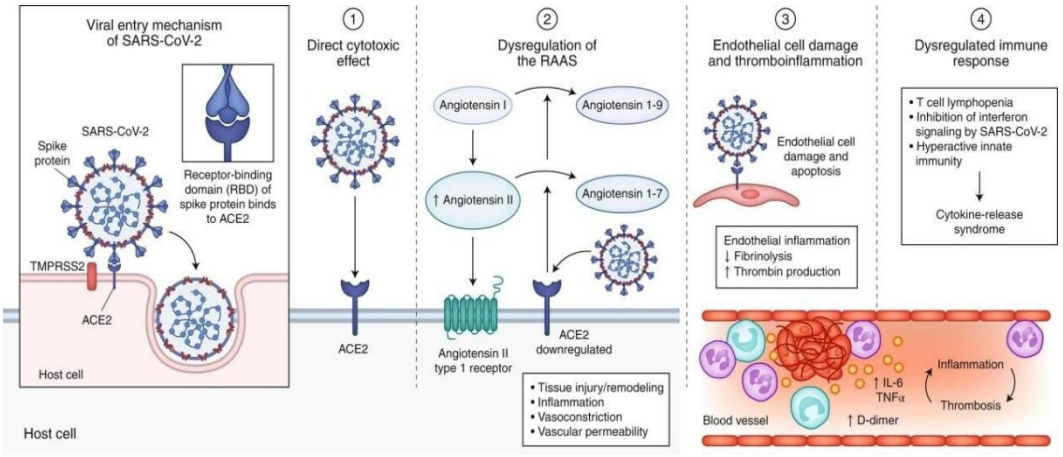

Fig. 1. Cytokine stromata,SARS-CoV-2 enters the host cells through the interaction of the protein spiny with the entry receptor ACE2 in the presence of TMPRSS2 (far left). Suggested mechanisms for COVID-19 resulting from SARS-CoV-2 infection include (1) direct cell damage by the virus; (2) Dysregulation of RAAS as a result of downregulation of ACE2 associated with viral entry, leading to decreased cleavage of angiotensin 1 and angiotensin 2; (3) Endothelial cell damage and thrombophilia. And (4) a defect in the regulation of the immune response and hyper-inflammation caused by inhibition of interferon signaling by the virus, depletion of T-lymphocytes, and production of inflammatory-stimulating cytokines, especially IL-6 and TNFα. [55].

After All of these immune reaction virus affected directly and indirectly the human cell cause multi system organ failure some people appeared as symptomatic or a symptomatic infection directly affected olfactory cell ten decrease smell, or damage gestation receptor leas to decreased in taste damaged mucosa pharyngeal cell lead to sore throat, and affected lung because viral pneumonia become potentially (Acute respiratory distress syndromes) progress systemic inflammatory response syndrome formed multi system organ failure specially heart lead to decreased of cardiac function may lead specific condition cardiac myopathy and since the cytokines circulated in the blood cause increased in the infiltration of fluid at the same time blood volume decreased cause hypotension which then decreased of profusion of blood to the organ also formed multi system organ failure which lead to septic shock [Kenneth,2020]

Angiotensin-converting enzyme 2,It is also expressed in many tissues outside the lung, including the heart, liver, kidneys, and intestine [Crackower,2020;Hamming,2004;Hashimoto,2012]. High levels of angiotensin converting enzyme 2 are present on the luminal surface of differentiated epithelial cells in the small intestine, while levels are lower in hollow cells and in the colon when virus infection leads to disturbance of intestinal secretion and absorption that appears in the form of abdominal pain and nausea. Diarrhea [FrançoisTrottein[1]HarrySokol,2020;Liang,2019]

This may indicate that consuming contaminated foods could spread the virus into humans. On the other hand, enteric expression of ACE2 may have fundamental effects on fecal-to-mouth transmission and thus bypass viral spread. As we have seen during previous coronavirus outbreaks, nearly half of COVID-19 patients have detectable RNA in their faeces - even when it is no longer present in the respiratory tract [Xiao,2020; Wang,2020]. After a lung infection, the virus may enter the blood and build up in the kidneys and cause damage to the resident kidney cells. Indeed, COVID-19 RNA was found in the plasma of 15% of patients by means of a real-time polymerase chain reaction [Huang*et al*,2020]. Modern human tissue RNA sequence data showed that EACE2 expression in the urinary organs (kidneys) was nearly 100 times higher than in the respiratory (lung) organs [Li Z*et al*.2020]. Therefore, the cause of kidney disease may be the entry of the Coronavirus into the kidney cells through a pathway dependent on the ACE-2. Second, the deposition of immune complexes may lead to the virus antigen or specific immune responder mechanisms induced by the virus (T lymphocyte or specific antibody) To kidney damage. However, microscopic samples of the kidneys from SARS patients have been reported to show a normal glomerular side and no electron-dense deposits [Chu KH,2005].

Further study. Third, the cytokines or mediators induced by the virus may exert indirect effects on renal tissue, such as hypoxia, shock, and rhabdomyolysis. In fact, some patients with 2009 H1N1 virus had mild to moderate elevations of creatine kinase in the blood [48] and since the emergence of covid19 receptors in the kidneys or by the formation of the Ab-Ag complex or by the effect of lead-releasing cytokines decreased in their performing functions. The kidneys lead to oliguria (decrease in urea production) directly or affect the kidneys indirectly due to the decrease in the abundance of blood to the kidneys, thus the kidneys' ability to get rid of creatinine in the blood decreased compared to the high creatinine in the blood which leads to mechanical damage to the renal cells and thus it was reported. It showed that 6.7% of SARS patients had acute kidney injury (AKI), and the mortality rate for those with AKI was 91.7%. [Chu *et al2005;*Huang*et al,*2020].

It is extremely expressed in the endothelial layer of small blood vessels, but not in the sinusoidal endothelium, however, the hepatic distribution of ACE2 is peculiar. [Chai*et al*,2020]. the ACE2 cell surface receptor was additionalexceedingly expressed in cholangiocytes (59.7%) than hepatocytes (2.6%). The level of ACE2 expression in cholangiocytes was parallel to that in type 2 alveolar cells of the lungs, representing that the liver might be a potential target for SARS-CoV-2[Qianyin,2020]. In liver covid19 damaged heptic cell results to increased permeability leading to the leakage of cytosolic enzymes and release specific inflammatory enzymes like AST ALT acute phase reactive protein, c-reactive protein Fibrinogen IL6 and Bile all these elevated in blood we can used these during diagnosis [Fan,*et al.* 2020,Sarhat,2019;Hoffmann, *et al*.2020].

CONCLUSION

This is the first study of COVID-19 in Kirkuk City, Iraq Whereas clear variations in different organs detected before and after each the introduction of At the end despite this .the effects of the COVID-19 paper, further works can be necessary under different laboratories inorder to progress and strengthen these data about COVID-19 as a potential pandemic for theheart, kidney,liver and intestine, which we recommended these organs effected due to immune response rather the than the protocol treatmenteffectsthat used with COVID19 patients.

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