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Corona Virus 2019 (SARS-COV2) and Chronic Diseases in France

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Abstract :

There has been a new global health crisis that threatens the entire world due to the advent and spreading of the new corona-virus 2019 (2019-n-CoV) or severe acute respiratory syndrome corona-virus 2 (SARS-CoV2). This virus has first originated in the bats and has been transmitted to the human beings by theyet unknown intermediary animals in Wuhan, China in Dec. 2019. the period of incubation ranges between 2 and 14 days.The signs of this illness are often cough, fever, shortness of breath, sore throat, malaise, fatigue,etc. Several people do not have any asymptoms. SARS-CoV2 infects people of any age, the elderly and the eople who already have medical conditions (like the diabetes and heart diseases) are at high risksto get severe illnessby this virus. Due to the lack of preliminary studies on the risk of infection of infected persons with chronic diseases with covid-19 in France, due to the large number of infections in the region, the paper aim to identify or diagnose the SARS-CoV2-19 virus and how it spreads in France .and its effect on the health of infected persons with chronic diseases and provide Health and preventative instructions for them to reduce their risk of infection. The mainobjective of the surveillance at this time has been supporting the worldwide strategy to contain SARS-CoV2 with the fast identifications and follow-up of the cases that are linked to the affected countries for the purpose of minimizingthe onward transmissions,ACE-2 is one of the known peptidases,it has the task of regulatingRAAS (i.e. renin-angioten-aldosterone system), thereby, it controls the pressure of blood. Which is why,it is no surprise that the initial reports have been suggesting that diabetes,hypertension and CVDshave been the most widespreadfactors of comorbidity in the SARS-CoV-2. This global pandemic produced a massiveamount of the literature on risk factors worsening clinical events that are related to this virus. In fact, not all the patients undergo this disease with equal degrees of severity, and some of them are evenasymptomatic. Diabetes rapidly became a potential factor of risk, COVID-19 Diabetic patients are under higher risksto

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develop severe pneumonia and get noticeable pro-thrombotic and pro-inflammatory states, in comparison with the infected individuals who do not have diabetes. In addition to that, they had as well considerably higher rates of mortality 7.80% vs. 2.70% in addition to a higherrates of multiple organ injuries. We conclude from that after the World Health Organization declared this disease a pandemic .. and there is no age category excluded from infection, as it affects young and old equally, especially the elderly, especially people with chronic diseases such as hypertension, diabetes, and cardiovascular disease more exposed to infection.

Key-words: Epidemic, Pandemic, Coronavirus SARS-CoV-2 (COVID-19), ACE2 receptor polymorphism, Hypertension, Diabetes , Cardiovascular diseases, Chronic Diseases , France

1-Introduction :

One of the single-strand RNA viruses that cause illness such as neurologic, hepatic, gastrointestinal as well as respiratory diseases in humans and even in animals are known as Coronaviruses (CoVs) **[1]**. So, coronaviruses that have the largest known RNA genomes, there are four genera of CoVs are gamma-, delta-, beta- and alpha-coronavirus **[2].** Six human coronaviruses (HCoVs) have been stated till then, such as Middle East respiratory syndrome-CoV (MERS-CoV) **[3]**, severe acute respiratory syndrome-CoV (SARS-CoV) **[3],**HCoVs-HKU1, the beta-CoVs HCoVs-OC43, HCoVs-229-E and the alpha-CoVs HCoVs-NL63**[4]**. The novel coronaviruses tend to arise regularly in humans, possibly associated with increased rates and widespread of coronavirus, the wide genetic variation and repeated recombinations of their genomes, and increased interface activities among animals and humans**[5,6].** Many local health authorities stated that there are patient clusters with an unknown cause pneumonia, who have been epidemiologically related to one of the seafood markets in China, Hubei, Wuhan in late December 2019 **[6].** Infectious agents, local hospitals detected a SARS-CoV-2with the use of a surveillance system for "pneumonia of unknown cause" developed in the aftermath of the outbreak of SARS in 2003 to allow timely detection of novel pathogens **[6,7]**. World Health Organization (WHO) announced on 30 January 2020 that CoVID-19 is "an international public-health emergency" **[8]**. The pandemic is on a fast progression. We reviewed the related SARS-CoV-2 literature to summarize the SARS-CoV2 infection preventions, diagnosis and treatments, clinical characteristics and epidemiology.

The present paper aims to diagnose or classify the SARS-CoV2-19 virus and how it spreads in France due to a lack of preliminary studies on the risk of infection of infected persons with chronic covid-19 diseases in France, due to the large number of infections in the region..

And its impact on the health of chronic disease infected persons and offers safe and prevention guidance to reduce their risk of infection.

2-Surveillance in the WHO European Region :

In December 2019 a pneumonia epidemic of uncertain origin was found in Wuhan , China**[9].** Chinese authorities announced on 12thJan. 2020 a sequence of thenew coronavirus named SARS CoV-2 that has been extracted from several clustered events **[10]** . Thence, the SARS-CoV2 disease was identified as Coronavirus Disease 19 (COVID-19).

At this time, the ultimate goal of surveillance was to assist the regional COVID-19 containment plan with accelerated detection and follow-up of the cases that are related to impacted countries so as to reduce dissemination forward. The objectives of surveillance used to inform country preparedness, to improve more case management and detection and to identify the primary clinical and epidemiological features of SARS CoV-2 cases that have been detected in the European countries. The data obtained contained demographic, background of recent travel to infected regions, near association with a possible or confirmed case of SARS CoV-2, underlying illnesses, symptoms and signs of the disease onset, type of the specimens from which the virus has been identified and clinical result. For surveillance purposes, case definition of WHO has beenaccepted: the confirmed case has been defined as an individual with lab confirmation of theCovid-19 infection (ECDC recommended 2 separate tests of Covid-19 RT-PCR), regardless of the clinical symptoms and signs, while a possible case has been a suspected case for which pan-coronavirus test was either inconclusive or positive **[11]**.

3-COVID-19 the First Cases in France:

On Jan. 7th, 2020 **[12],** a newSARS CoV-2 triggering a set of the respiratory infections (COVID -19) was detected in Wuhan. Initially 27 patients with pneumonia were reported having an epidemiological relation to a live animal market, which has been closed then disinfected on Jan. 1st**[12].** By Jan. 20th, the amount of the case reports grew significantly, and by Feb. 12th2020, there have been 45179 Covid-19 cases, which includes 1116 death cases confirmed**[13].** In 31 Chinese autonomous regions and provinces many cases have been recorded as well as more than 514 cases were recorded in other countries in North America, Europe, Australia and even Asia**[13].** The primary source of infection remained unclear till now, and may still be active.. Shortly after the appearance of Covid-19 in China and abroad, human-to - human transmission including healthcare settings and family clusters was observed. The existing features of the epidemic clearly suggest a constant human-to - human spread..**[14].** On 10 January 2020,

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strengthened oversight of SARS Cov-2 cases has beencarried out in France. The surveillance aims at early identification of imported cases and avoiding secondary transmission, whether among healthcare workers (HCW) or in the community. Investigations are performed among contacts shortly after the occurrence of illness and a follow-up protocol has been undertaken based on the degree of risk of infection assessed. Here we identify real-time implementation of this system of surveillance for the first 3 imported COVID-19 cases that have been found in France which were reported in individuals with a recent stay in Wuhan on 24 January 2020.Two test reports were made in Paris and one in Bordeaux. We are providing reports on the follow-up of the contacts of the cases started right after the diagnosis of this infection until 12th of February **[14]**.

4-The Surveillance System and Detected confirmed cases in France :

In France, they determine how the patient meets the conditions for a potential case throughout case description. If they do, the case will be notified to the Department of Regional Health (Agence Regionale de Sante - ARS) directly via a 24/7 telephone line, which alerts the hospital infection prevention teams engaged in patient care, French Public Health Service and the Ministry of Health without hesitation **[14].**A systematic inquiry method gathering socio-demographic knowledge , clinical data and experience background (background of residence in or travel to Wuhan or interaction with a reported event) is conducted at regional levels, in cooperation with ARS, SpFrance, and clinicians for each potential case.Data have been entered in secure Voozanoo (Epiconcept, Paris) Web-based application. Possible patients must be treated, cared for and segregated in one of the 38 French rehabilitation clinics approved by Ministry of Health according to the Middle East respiratory syndrome (MERS) treatment guidance **[15]**. The respiratory samples from lower respiratory tract (i.e. bronchoalveolar lavage fluid, if indicated, or induced sputum) and from the upper respiratory tract (i.e. nasopharyngeal swabs or aspirates) have beenobtained and sent to one of the accredited labs for the purpose of performing SARSCoV-2 specific RT-PCR in real time for each possible case.Only the National Reference Center for Respiratory Viruses (Pasteur Institute) had been capable of testing for the presence of the SARSCoV-2 until 27 January **[14]**.

Between the 17th and 29th of Jan. 2020, a possible case has either been characterized as a patient who has a serious acute infection of the lower respiratory tract who required hospital admission and a history of residence in or travel to Wuhan, during 14 days prior to the start of the symptoms, or a patient with an acute respiratory condition irrespective of seriousness and risk exposure history, specifically to a reported event. A verified case has been identified as a

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potential case that has been conducted by an approved laboratory with a positive Covid-19 RT-PCR on the respiratory samples. The testing was based on the RT-PCR protocol established by the Charité in real time **[16]**. In addition tousing RT-PCR sensitive in real-time for Rd-Rp gene (4 targets) developed at the Pasteur Institute (RdRp-IP). The case description has beeninitially defined on Jan. 10, and modified over the time. The comprehensive case description that has been utilized for cases that have been discussed here are included in Supplement as well as the current up-to - date case concept **[14]**.

There have been 9potential casesthat have been characterized in France from 10th to 24thJan. (period until the confirmation of 1stcases in France); among them, three cases have beenrecorded with coronavirus disease 2019. Case1 has been a male patient who was aged 48 years who was living in France. He flew to different locations in China for professional reasons, including Wuhan, before he felt the first signs on 16 January (cough, fever and headaches). On 22 January he flew back via Shanghai, Qingdao and Paris Charles de Gaulle airports to Bordeaux, France. Throughout the flights he has mentioned wearing a mask. He received medical treatment from a general practitioner on 23rdJan., where he has been expected of being ill with SARS Cov-2, and eventually referred to the national referring hospital of Bordeaux, extracted and tested for laboratory evidence of SARS-CoV-2 infection **[14].** National Reference Centres (NRCs) reported the infection on 24 January: Regular reports have also been released on the SpF website. The three cases were reported to European Commission on 26 January by the Early Warning and Response System (EWRS), and to European Center for Disease Prevention and Control (ECDC) on 28 January by the European Surveillance System (TESSy) **[14]**. This disease has beenconfirmed as pandemic by WHO on 11thMar. 2020 **[17].**

5-COVID-19 and Chronic Diseases in France :

Seven coronaviruses which are responsible for some serious respiratory diseases were identified in humans during the past 20 years. Many of them, like Covid-19 (beta coronavirus lineage b / sarbecovirus), may result in lung damage to patients and often multi-organ dysfunction with adversarial myocardial re-modeling, cardiomyopathy and myocardial stress **[6,18].** Covid-19was recently identified as a human angiotensin I, which transforms enzyme 2 (ACE-2)-tropical virus **[19].** Capable of attaching alveolar pneumocytes to their surface that transmit ACE2 **[20]**. In the humans, however, ACE-2 mRNAs have been defined to be expressed in virtually every organ, including testicles, kidneys, the heart, and blood vessels, which open up the potential for the virus to invade other tissues beyond the lungs**[21].** ACE-2 can be defined as a recognized peptidase, regulating the mechanism of RAAS and hence influences the blood

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pressure. It comes as no surprise that cardiovascular, diabetes and hypertension diseases according to the initial reported that suggested that the most frequents of these diseases comorbidity in COVID-19 disease **[22]** .

5.1-Hypertension and COVID-19 :

It looks possible that the susceptibility to the SARS-CoV2 and COVID-19 disease may be influenced by the polymorphism of the ACE-2 gene, human ACE-2 m-RNA expression and human ACE-2 protein polymorphism.The attachment of gp-120 viral envelope glycoprotein to CD-4 receptor has been demonstrated for over 20 years in the human immunodeficiency virus (HIV) field, a retrovirus which is transmitted through the sexual intercourse**[23].** to CXCR4 **[24].** or CCR-5 co-receptor **[25]**. triggers the signaling of the cell. The permanent molecular cross-talk between the cell and the cell's environment plays a crucial role in these molecules.The study of CCR5 coreceptor polymorphism in this viral model clearly showed that a normal deletion of D32 prevented HIV infection in homozygous people who carry that genotype **[26]** . For the MERS-CoV, spike (S) glycoprotein attachment to the human cells requires host cell typeII trans-membrane di-peptidyl peptidase protein 4 (DPP-4 / CD-26) **[27].**After interacting with DPP-4, MERS-CoV 's S protein undergoes proteolytic activation once inside endosomes via the cysteine protease cathepsin L and cellular serine protease TMPRSS-2 **[28].**

Kallikrein-related peptidase 5 (KLK-5) may release soluble forms of DPP4 into the bloodstream after cleavage **[29].** Recently it has been reported that amongst14identified mutant types of DPP-4, 4 polymorphisms (which are K267N, K267E, D346-348 and A291P) significantly reduce the MERS-CoV binding and penetration in the target cells and viral replications**[30].** With respect to SARS-CoV, the spike protein's S1 domain mediates ACE-2 receptor binding while S-2 domain can be described as a membrane-related portion whichwillpossibly undergo postbinding trans-conformational alterations that allow the fusion of the membranes. Viralreceptor binding domain (RBD) that is located in S-1 was reduced to 318 to 510 amino acid residues **[31].** A Coe crystal structure from the ACE-2 to the RBD has shown that the residues between 424 and 494 are in a direct contact to the 1sta-helix and Lys-353 and proximal residues at ACE-2 terminus b-sheet 5N **[32]**. Through the alteration of His-353 amino acid in the ACE-2 of the rats and throughthe alteration of the site of glycosylation (Asp90), which has the ability of altering ACE2 a-helix 1 conformation, Li and colleagues **[32]** . Decided to turn the ACE2 rat into an efficient receptor of the SARS-CoV. A Leu584Ala point mutation in ACE-2, significantly mitigated the enzyme shedding and facilitated the entry of SARS-CoV in the target cells **[33].** A soluble ACE-2 form, lacking the cytoplasmic and tran-smembrane domain of the molecule's has beenstated to have the ability of blocking SARS-CoV spike protein

binding to ACE-2 **[34].** Regulated ACE-2 expression was noticed in the cells that have been infected with the SARS-CoV **[35].** A recombinant SARS-CoV spike protein has beendiscovered to be degrading the regulated ACE-2 expression through the release of the sACE-2 and as a result, promoting the injury of the lungs **[36].** Amongst other anti-viral chloroquine impacts upon the SARS-CoV in vitro, a glycosylation deficit of ACE-2 virus surface cell receptor may be attributed **[37].**Regarding HCoV-NL-63 that utilizes the ACE-2 as well for the cell entry, recombinant SARS-CoV / HCoV-NL63 spike protein trigger for the shedding of sACE=2 **[38].** Lately, the research of the cell entry of covid-19 through the ACE-2 binding has shownconsiderablesimilarities between the infections of SARS-CoV and SARS-CoV2, which include similar selection of the entry receptor **[39].**

The SARS-CoV2 S1 trimeric spike binds ACE2 PD domain and the ACE-2 C-terminal segment (residues 697 - 716) cleavage by serine 2 trans-membrane protease (TMPRSS-2) improves S-protein-driven viral inputs. Through the comparison of 805 amino acid residues of the ten human ACE-2 proteins and the fourdistinct isoforms of the ACE-2 that are available through the GenBank with the use of the Clustal Omega multiple sequence alignments, a 100% identity has beennoticed amongst complete sequences of the ACE-2, and those isoforms have been corresponding to deletion in the domain of the CLD or trans-membrane truncation. The impact of those isoforms is stillunclear in SARS-CoV2 and COVID-19 infection outcomes. As stated by Cao and his colleagues recently worked **[40]**. 32 ACE2 variants where 7 variants of the hotspot (Ile486Val, Lys26Arg, Asn638Ser, Ala627Val, Asn720Asp, Ser692Pro, and Leu731Ile / Phe) are characterized in a variety of the populations, which opens the possibilities that particular people may have less susceptibility to the SARS-CoV2 compared to the others. The ACE-2 protein on the surface of lung alveolar epithelial cells helps SARS-CoV-2 to infect the respiratory tract. It may be assumed that the levels of the ACE-2 are correlated with the susceptibility to the SARS-CoV2 infection. Supposedly, the males have higher expression of the ACE-2 in lungs compared to thefemales and Asians have higher ACE-2 expression compared to the Caucasians and African American people **[41].** It is in line with the finding that the ACE2 's conversion of the Ang II into Ang (1e7) was higher for males than for females **[42].**Suggesting men to have overexpression of ACE-2. Since ACE-2 is encoded with a gene that is located on X chromosome and the maleshave higher expression of the ACE-2 compared to the females, it may be hypothesized that they may be considered less susceptible to the most serious adverse effects of the infection depending on the allele expressed by women **[38,43].**

All the clinical studies released up until now indicate that the males constitute 66 to 75 percent of COVID-19's most serious cases. Throughout the early infection with SARS-CoV2 and

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viral spread in the tissues of the body, ACE2 function will possibly be impaired either through the steric hindrance of the ACE2 peptidase domain after the binding of the virus or through decreased regulation of the expression of ACE-2 m-RNA and ACE-2 proteins. In the extreme disease of COVID-19, the existence of viral receptor may be explaining multi-organ failuresthat are often seen in the clinic on other tissues than the lung. Therefore we recommend incorporating ACE-2 and AngII quantification to the biological monitoring of patients who have COVID-19. ACE2 has been known to be able to shift the balance of the RAAS by converting AngII to Ang (1e7).Consequentially, COVID-19 and HT have lately become a matter of concern for the professional international cardiology societies with respect to: a. the HT patients' susceptibility to the COVID-19; b. disease severity; c.using ACEi and Ang II receptor blockers (ARB targeting AT1R). HT inhibitors are known to increase the expression of ACE2 on the cell-surface. ACEi has been shown to increase bowel ACE2 mRNA expression **[44]** .

Though data on the effects of these medications on the expression of ACE-2 mRNA in the epithelial cells of the lungs are rare, there are concerns that the patients who receive those treatments may be supportingthe capture of the virus.Amongst the patients with HT, receiving treatments with the long-term olmesartan (ARBs), the levels of the urinary ACE-2 have been higher compared to it in the untreated controls**[45]**. By comparison with HT, expression rates of ACE2 in patients with idiopathic pulmonary fibrosis decline markedly **[46]** . ACE2 is an significant player in inflammation and fibrosis resolution **[47].** In experimental model of the bleomycin-induced pulmonary fibrosis, intraperitoneal injection therapy with the recombinant human ACE-2 resulted in the increase of the lung function and decreased fibrosis and inflammation in the lungs **[48].** In addition, impaired ACE-2 Ser-680 phosphorylation by the AMP-activated protein kinase in results of the pulmonary endothelium in labile ACE-2 and as a result the pulmonary HT **[49].**Attention has to be paid to the molecules that include the dimiazene aceturate (DIZE, an antitrypanosomal drug) and xanthenone (XNT), which have been characterized as ACE-2 activators **[50].**SubcutaneousDIZE infusion in an ischemic heart disease of the rat model has resulted in substantially enhancing theexpression of the cardiac ACE-2 mRNA and the catalytic function of the ACE-2 protein, reduced expression of the ACE mRNA and strengthening the cardiac remodeling **[51].** It is therefore important to examine the potential advantageous characteristics of specific molecules like the exenatide (one of the glucagon-like peptide-1 agonists) that cause increased vasodilatory and decreased vasoconstrictive mediators **[52]** . Additionally, heparin (anticoagulant) therapy has recently been documented to be correlated with reduced mortality in the extreme COVID-19 coagulopathic patients **[53]** . In a Chinese cohort of 1099 COVID-19 patients, 165 (13%) individuals were HT patients, 24% of

whom suffered from severe COVID-19, 3.70%, a little bit higher than general COVID-19 patient population. **[54].** In a smaller sample of 191 COVID- 19, 58 (30 percent) patients were with HT and 48 percent of those patients have died, and that is considered surprisingly high (i.e. 14.6 percent) **[55]** . Such findings indicate that in patients who acquired serious COVID-19 illness, the proportion of patients with HT was greater than the ones that don't. By the middle of Mar. 2020 the international cardiology professional societies have recommended continued treatment of the patients**[56]**. Additionally, when spike SARS-CoV2 binds the ACE-2 receptor in the area of helix1 (Lys 31, Tyr41) and b5 (Lys353), it possibly reduces the catalytic ACE-2 characteristics, which areusually correlated with decreased inflammation. Failure to produce Ang (1e7) will result in increasing the lung injuries**[57,58]**. And cardio-vascular risks, AngII functions as inflammatory cytokine **[59]** . It was found in a murine model that lung inflammation results in the aggravation of the AngII-induced abdominal aortic aneurysms **[60]**. The mutations may alter the degree of ACE-2 protein expression, as can be seen in the murine model **[61].**Deleting the ACE-2 in the mice model has been correlated with enhanced rates of AngII circulation and tissue and induced cardiovascular harm **[62]** . It is likely that a) the mutations influence human gene ACE-2; b) transcriptional variability in the expression of ACE-2 mRNA; c) post-transcriptional alterations operating on viral ACE-2 receptor (like the N-glycosylation); d) mutations in the putative ACE-2 protein may result in affecting the outcomes of COVID-19 through acting on the blood pressure through the RAAS and potentially resulting in the increase of the heart and lung damages via Ang II oxidative stress. SARS-CoV-2 fatality has recently been reported in Iran **[63].** Any fair justification. If it is necessary to eliminate underreporting of the amount of infected individuals, it may be hypothesized: a) a more violent SARS-CoV-2 variant clade **[64]** . ; (b) A difference in ACE-2; or (c) gene variability such as Tolllike receptor encoding. Since Ang (1e7) is considered to prevent the inflammations through the inhibition of resistance in / TLR-4/MAPK / NF-kB path-way **[65]** . And that the gene TLR4 is extremely variable in various ethnic groups in Iran **[66].** It remained likely that the SARS-CoV2 causes increased inflammations in the Iranian patients through the suppression of the AngII to Ang (1e7) with ACE2-mediated metabolism. This may be linked to the finding that mice defective in TRIF adapter TLR3 / TLR4 have extreme susceptibility to the SARS-CoV infection,which includes the extreme inflammatory inductions**[67].** The process of acute myocardial injury, which is induced by the SARS-CoV2 throughout the serious COVD-19 may be linked with the catalytic activity inhibition of the ACE-2 **[68](Fig. 1).**

Intriguingly, a new report has been released as a pre-print publication **[69]** . A list of 97 licensed medicines, including statins (i.e. simvastatin),antidiabetics (i.e. metaformin), and ARBs

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(i.e. sartans), may have therapeutic efficacy against COVID-19. The medical data of the patients that are being currently treated using those compounds can be helpful for the identification of whether or not those drugs have positive or adverse impactsupon the COVID-19 patients.In a different research, the metaformin has beencharacterized as well, as one of the potential drugsfor repurposing the SARS-CoV2 **[70].** It has to be kept in mind that the large amounts of the data have suggested that in the patients who have the severe case of the COVID-19 there is a severe or a mild cytokine storm that is one of the significant death causes. It can be making sense to keeptreat the patients who have the ACE inhibitors and the ARBs for the purpose of reducing pro-inflammatory effects of the AngII and cytokine storm that has been noticed in the severe COVID-19, one of the conclusions that have beencommonamongst thelatest recommendations from the international societies of cardiology **[71]** .However, Fang and colleagues **[58]** .

Do those molecules harmfully affect theresult of the disease or has the link been made by highlighting only a confounding aspect,confirming that the hypertension is one of themain factors of comorbidity? According to others**[72,73]** . We consider rapid assessment of whether or not those medicationshave more positive than adverse impactson the patients who havethe severe cases of COVID-19 to be of particular importance.

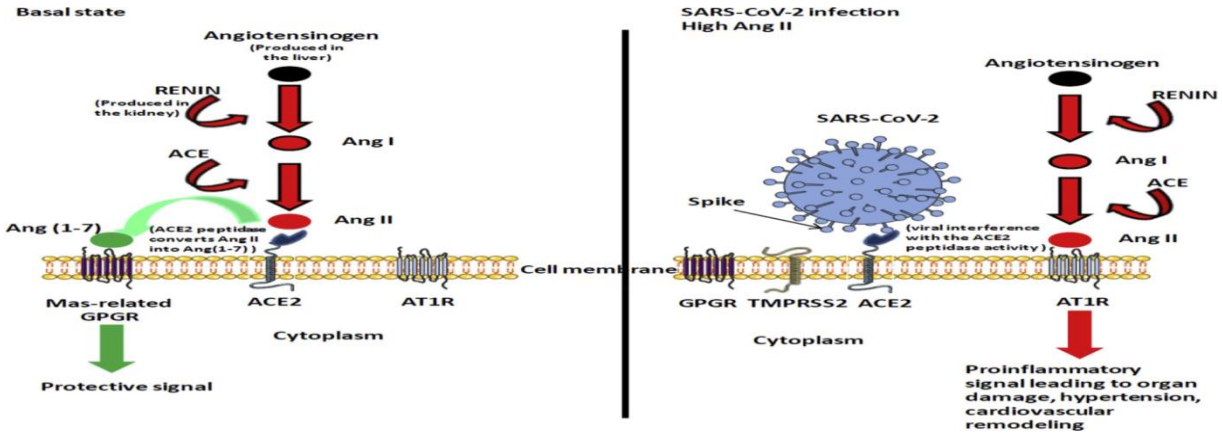

Figure 1. Simplified diagram of renin-angiotensin system under the pathogenic and normal conditions. The left panel exhibits that the ACE-2 performs the conversion of the AngII to Ang (1e7) thatresults in a protective signal. The right panel showspotential dysfunction of the signal in the case of the attachment of the SARS-CoV2 to its ACE-2 receptor. Under such condition, the Ang (1e7) is not synthesized anymore, AngII will accumulate and bind the AT1R, which results in the pro-inflammatory signals whichresult in damages to both tissues (especially the heart and lungs) in addition to the hypertension[68] .

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5.2-Diabetes and COVID-19*:*

The pandemic of COVID-19 culminated in a massive amount of the literature on risk factors exacerbating virus-associated clinical incidents. Nevertheless, not all people experience the same difficulty of the disorder, so certain people are asymptomatic. Diabetes quickly becoming a main risk factor? Was diabetes a cause of resistance, and/or severity? If so, will antidiabetic drugs, especially inhibitors of dipeptidylpeptidase4 (DPP4), have an impact on the infection?

Although diabetes does not actively raise the risk of becoming diagnosed with COVID-19, a chronic variant of the disease would possibly evolve if diagnosed patients with diabetes. A meta-analysis of 6researches in China have discovered that relative risks of the severe casehas been 2.26 (95percent CI: 1.47—3.49); varied from 0.31 (lower risk in one of the studies) to 4.06 (higher risks in 5researches) **[74].** For instance, in a Chinese retrospective sample that included 1,000 patients with a reported illness, diabetes' prevalence in these cases with the serious disease has been 16% and only 5.50% in the ones with lower severity of the disease **[54].** For another survey of 1043 Italian patients who were compromised and treated for ICUs in Lombardyin, 2/3 had one of the causes of comorbidity, 17% had diabetes and 49% of them had HT **[75] .** In Italy, a longitudinal study that included 1,362 diabetes patients have culminated in a little bit elevated probability of referral to the ICU (OR 2.79, 95percent CI: 1.85-4.22, P < 0.0001) and decreased risks of death (3.21, 95 percent CI: 1.82—5.64, P < 0.0001)**[76].** In a Chinese retro-spective sample of 323 patients they were more prone to have negative results (OR = 3.10, 95 percent CI: 1.16—8.37, P = 0.025) **[77]** . After that, 58 per cent of the 24 patients committed to the ICUs became diabetic in Seattle **[78]**. Coinciding with those reports, a meta-analysis that has been performed on 6,452 diabetic patientshas shown that the diabetes has beenrelated to the composite poor outcomes (which include severe COVID-19, mortality, need for ICU, acute respiratory distress syndrome, and progression of the disease)[RR2.38, 95% CI: 1.88-3.03, *P* <0.001], acute respiratory distress syndrome (RR4.64, 95% CI: 1.86-11.58, *P* = 0.001), severe COVID-19 (RR2.45, 95% CI: 1.79-3.35, *P* <0.001), and progression of the disease (RR3.31, 95% CI: 1.08-10.14, *P* = 0.04). Meta-regression has shown that the age (P = 0.003) and obesity (P < 0.001) affected the relationship with composite negative result**[79].** Non-survivors have a higher incidence of diabetes mellitus in the global retrospective sample of 8,910 COVID-19 patients in Japan, North America and Europe. Yet DMhas not been one of the independent indicators of patient mortality in a multivariate study **[80]**. COVID-19 diabetic patients are at elevated risks of a serious pneumonia and show a pronounced pro-thrombotic and pro-inflammatory condition relative to the patients who do not have the diabetes which become compromised.Inflammation

indicators like theferritin ferritin, CRP, Il-6, and D-dimers are improved relative to the patients that are not diabetic, whereas a reported inflammatory or cytokine storm is believed to be correlated with more pejorative prognoses **[81].**

High age was separately correlated with a serious type in a study and meta-analysis of 15 researches that involved 51845 COVID-19 patients, 9,066 of which have been extreme forms**[82].** Diabetes has been also correlated in this study to the frequency of a severe case with 2.81RR (95 percent CI: 2.01-3.93), and that correlation continued in a multivariate analysis study that takes under consideration the age (RR2.21, 95 percent CI: 1.33-3.66, P = 0.002) **[83].** The incidence of the serious type has also risen with the advent of unbalanced or complicated diabetes in 2009 case trials with H1N1 viruses and 2012 with Coronavirus Respiratory Syndrome in the Middle East (MERS-CoV) **[78,79,80].** In a longitudinal prospective analysis from March 1 to April 6, 2020, the rate of mortality has been 28.80% in the diabetes patients and/or unregulated hyperglycemia, relative to 6.20% in patients who do not have hyperglycemia or diabetes (P < 0.001). In a sample of 7,336 COVID-19 patients from 19 Hubei hospitals with or without diabetes, patients were admitted to hospital with the COVID-19 and required additional medical treatments. Given such measures, they have saw slightly higher death rates: 7.8% vs 2.7%, as well as a larger frequency of recurrent injury to the organ. Well-regulated blood glucose patients (glycemic variation below 3.90 to 10mmol / L) have slightly reduced mortality relative to patients with badly managed blood glucose (glycemic volatility over 10mmol / L)[altered HR, 0.14; 95 % CI, 0.03-0.60, P = 0.008] throughout hospitalizations**[84]** . Those COVID-19 patients suffering from untreated hyperglycemia have an especially high rate of mortality. Various immune system defects were documented to clarify the connection between the immune dysfunction and the hyperglycemia, which include deficiency of polymorphonuclear and monocytic white blood cell phagocytosis and chemotaxis, complementary activity and cytokine deregulation **[85]** . These have remained to be proven that the acute hyperglycemia has animpact thatmay be strengthened through successful glycemic control. In another sample of more than 500 coronavirus patients, hyperglycemia was often intermittent and usually resolved in the majority of subjects following hospital discharge **[86]**. In most cases, the writers recommend that clinicians will manage hyperglycemia to reach BG levels < 180mg / dL **[85]** . Klonoff and associates have recommended 4factors of risk that could raise the likelihood of adverse results: corticosteroid treatment vulnerability to hyperglycemia, insufficient glucose control, lack of communication with health care providers and sufficient stoppage of the blockers of the angiotensin receptors**[87]** . CORONADO is a current French study that has been aimed at defining risk factors for serious disease types around the world **[88]**.

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5.3-patients with cardiovascular diseases and COVID-19:

By the end of Dec. 2019, a new corona-virus with zoonotic origin appeared in China, spreading quickly throughout the world **[6.7]**. impacting a significant number with countries at the time where this study has been published (at the beginning of Mar. 2020). SARS-CoV2 is an enveloped β-coronavirus RNA with a phylogenetic similarity to a different known corona-virus, which SARS-CoV, which hasresulted in the outbreaks of SARS in the year of 2003 **[89]**. Even though the clinical and epidemiologicalcharacteristics of COVID19 aren't entirely known yet, initially, the data suggestedsignificant consequences for cardiologists and cardiovascular system **[90]** .

Initially, the first case studies have shown that, once diagnosed to have SARS-CoV-2, the patients who have underlying or existing cardio-vascular disorders are at a greater risk for experiencing serious symptoms. In a study on 138 COVID19 patients hospitalized in Wuhan **[91]** . 64 patients (i.e. 46.40%) had one or several medical conditions which coexisted, mainly cerebrovascular or cardio-vascular. HT had resulted in 31.20% of cases, asthma in 10.10%, and CVD in 14.50%**[91]** . Intriguingly, these rates were dramatically greater in those with the most extreme COVID-19 manifestations (in other words, involving hospitalization in an ICU), with 58.3% obesity, 22.2% diabetes, 25% coronary disorder and 16.7% cerebrovascular disease **[91]** . Similarly, although the true average COVID-19 mortality rate remains undetermined and is calculated (according to a combination of approximate mortality) to be from 3to 4%, it may be even higher in the older patients (older than 60) or the patients who have pre-existing comorbidity cases like the diabetes (7.30%),coronary disease (10.50%), or HT (6%) **[92]**. Although the condition may manifest as a pulmonary disorder, the risk of case-fatality in patients with underlying coronary disease is higher (10.5%) than in the patients who have underlying chronic respiratory disease (6.30%) **[90]**.

Then, while COVID19 usually demonstrates signs of the infection to the lower respiratory tract, a large rate of the patients demonstrate cardio-vascular signs when initially presenting **[68].** These indications include palpitations and tightness to the throat, in particular. Furthermore, SARS-CoV-2 is also known to trigger myocardial injury. An rise in high-sensitivity cardiac troponin I (cTnI) was reported in 10-20 percent of COVID-19-infected patients **[18,91]** . In China, an additional 11.80% of the patients who have died due to COVID-19 have suffered severe heart injury, with increased rates of cTnI or cardiac arrest throughout the hospitalization, without any pre-existing CVD**[68]**. The precise factors contributing to acute myocardial damage are still uncertain but may be related to either acute myocardial-ditis or acute coronary syndrome, as historically encountered with the corona-virus diagnosed with MERS-CoV**[68]**. It

was noteworthy that traditional signs and the incidence of acute myocardial infarction in COVID-19 may be over-shadowed, contributing to a possible pause in diagnosis **[90]** . Overall, these first results show a degree of association, either explicitly or implicitly, between SARS-CoV-2 and the cardiovascular system. Infections with SARS-CoV and SARS-CoV2 are caused by attaching the spike protein of the virus to the ACE-2**[39]** . ACE2is a membrane-bound zinc metallo peptidase that engages in angiotensin cleavage. ACE-2 is expressed highly in lungs as well as in the heart, while the vascular endothelium, macrophages, myocytes and smooth muscle are located **[93].** Intriguingly, ACE2 is a post-myocardial infarction feature **[93].** And two groups with a greater likelihood of producing extreme variants of COVID-19 in patients with diabetes **[94]**. ACE2 frequently controls essential metabolic and cardiovascular functions, which include the blood pressure control and glycaemia **[95]** . This remains to be investigated if SARS-CoV-2 has a direct impact on the cardiovascular system by attacking ACE-2-expressing cells. Another hypothesis includes an downstream influence of SARS-CoV-2 immune reaction on the myocardium and on the vessels. Extreme types of COVID-19 are likely to include acytokine wind, and that affect the coronary plaque instability, as it has been observed earlier with the SARS-CoV **[96]**. Patients that have been diagnosed with SARS-CoV or SARS-Cov2 often have lymphopaenia **[18,91]**. A disease related to the growth of atherosclerosis and cardiovascular adverse effects **[97].**

The COVID-19 epidemic scenario is changing quickly, with clinical and physiopathological profiles unclear. The first case studies , however , show that COVID-19 has serious impacts on the heart and arteries which the cardiovascular community may learn about.

6-Conclusions :

From this we conclude that SARS-CoV2 outbreak occurred in France from 17 to 29 January 2020 and the World Health Organisation (WHO) announced this disease pandemic on 11 March 2020. We also assume that people with chronic disorders (hypertension , asthma, cardiovascular conditions) are people.It has been shown recently that the spike protein SARS-CoV2 binds to the human angiotensin I which converts ACE-2. This molecule is a peptidase, which is expressed on the surface of epithelial lung cells and other tissues regulating the system of renin-angiotensin-aldosterone. The rates of expression of the cellular ACE2 are not equivalent for humans. Additionally, polymorphisms of ACE2 have recently been identified in humans. Here we study the latest evidences that the polymorphism and/or expression of the ACE2 may affect both people's susceptibility to SARS-CoV2 infection and the result of COVID-19.More studies of the virus interaction, the peptidase activity of the ACE-2 as well as the rates of

angiotensin II in patients infected with SARS-CoV2 will help better understanding the pathophysiology of the disease and the multi-organ failures found in serious COVID-19 forms, especially heart failure.

The present paper illustrates that while there were not any significant safety issues linked to COVID-19 and the usage of glucose-lowering drugs in diabetes patients, there is very limited knowledge regarding the possible advantages or dangers of such agents in the case of COVID-19 infections.This paperupholds that DPP-4 inhibitors, GLP-1R agonists, SGLT-2 inhibitors and metformin have to be utilizedcarefully or withdrawn after admission to hospital of psychotic patientsand seriously ill patients. Insulin is commonly frequently used in patients with chronically ill diabetic hospitalizations, and in the patients with concomitant sepsis. Which is why, insulin is the most appropriate therapy in those cases, in particular, for the patients that have been hospitalized in ICUs where it is essential to discontinue certain glucose lowering medications.Careful consideration must be paid to avoiding hyperglycemia. The loss of physical exercise and nutrition attributable to lockdown and COVID-19 contamination are two conditions that may exacerbate the regulation of glycemia. This is important for all hospitalized and outpatient patients with diabetes practice proper control of blood pressure and establish daily interaction with their health care provider.

None-the-less, the first case reports have indicated the fact that COVID-19 has significantimpacts on the vessels and the heart, which have to be known by cardiovascular community. They are more vulnerable to infection with this virus and by providing health and preventive instructions and instructions reducing their risk of infection.

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