Nat. Volatiles & Essent. Oils, 2021; 8(6): 4862-4874

NVEO
Natural Volatiles &
Essential Oils

Evidences For Systemic Effects Of Covid 19 Pandemic A Literature Review

Dr. C.M.Anitha[1] , Dr. P.S.G Prakash[2] , Dr. Deepa Ponniyan[3]

[1,2,3]Department of Periodontics, SRM Dental college, Bharathi salai , Ramapuram , Chennai.

ABSTRACT:

The world threatening covid19 disease by SARS COV2, has emerged its origin from Wuhan china in November 2019. The disease has many systemic effects starting from oral cavity to urinary system including eyes and skin. The effects on the respiratory system with severe acute respiratory syndrome is more life threatening. The serious illnesses of the cardiovascular system and central nervous system includes Myocardial infarction and stroke. Acute Kidney Injury(AKI) is common which may require dialysis in most of the patients. Diarrhoea is the most common symptom of the gastrointestinal system and some patients experience severe abdominal pain. Conjunctivitis or" pink eye" is more common in eyes and is self limiting. The five clinical patterns of skin lesions includes vesicular , utricarial , macula papular, livedo/necrosis and pseudo-chilblains. Patients with severe covid 19 experienced both Exanthems (skin lesions) and Enanthems (oral cavity lesions). Multiple pin point petechiae like ulcers are seen in the oral cavity. Some of them experienced geographic tongue, Xerostomia, Gingivitis and opportunistic fungal infections because of the impaired immune system and susceptible oral mucosa.

Key words: SARS COV2,Covid 19 Pandemic,ACE2 Receptors, Spike protein ,AKI(Acute Kidney Injury), dys executive syndrome.

INTRODUCTION:

Corona viruses in general are RNA viruses having four genera, among which the alpha and beta corona viruses infect humans..SARS COV2 belongs to the family Corona viridae and order Nidoviridales. Corona viridae is again sub classified into Corona virinae and Toro virinae [Figure 1]

Figure 1: Classification of Corona virus

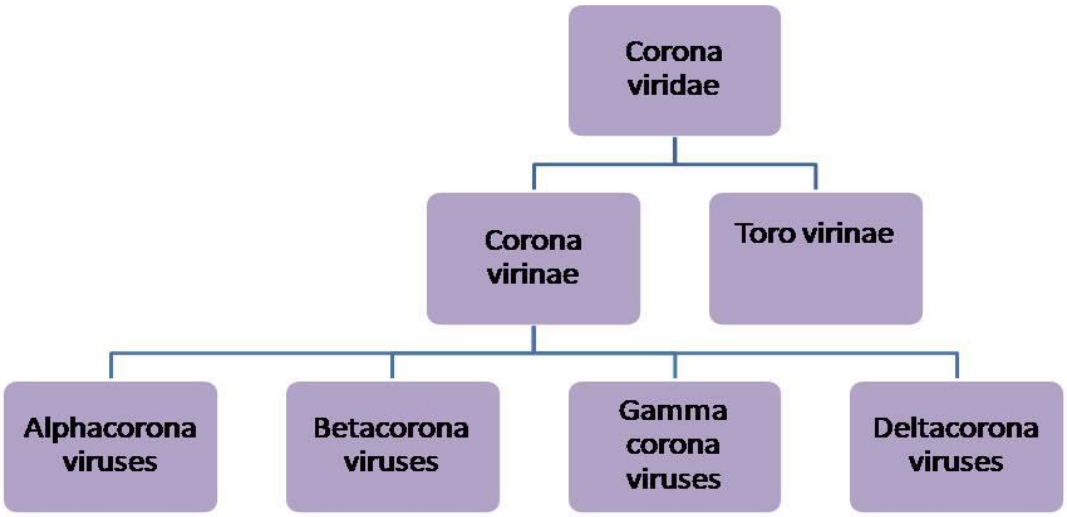


Figure :1 Classification of Corona virus

The corona virinae includes alpha corona viruses, beta corona viruses ,gamma corona viruses, delta corona viruses. The beta corona viruses are HCOV-OC43,SARS HCOV,MERS COV and SARS COV2.[1]

SARS COV2 is an enveloped positive sense single stranded segmented RNA virus that infect humans.[2]Generally the size of the corona virus ranges between 26 and 32 Kb.

EPIDEMIOLOGY:

The novel corona virus 2019 was identified in the city of Wuhan, central Hubei province in china. Later in November 2019 a suspicion of covid- 19 origination from bats was identified. Based on the studies of Genetic variation it was suggested that the main host reservoir is bats and further studies on glycoprotein analysis suggested that snake hosts could also be possible transmitters.

Later on in December 2019, clusters of cases of pneumonia were reported in Wuhan and on January 9th it was identified that the main reason could be the novel corona virus by various lab investigations including deep sequencing.

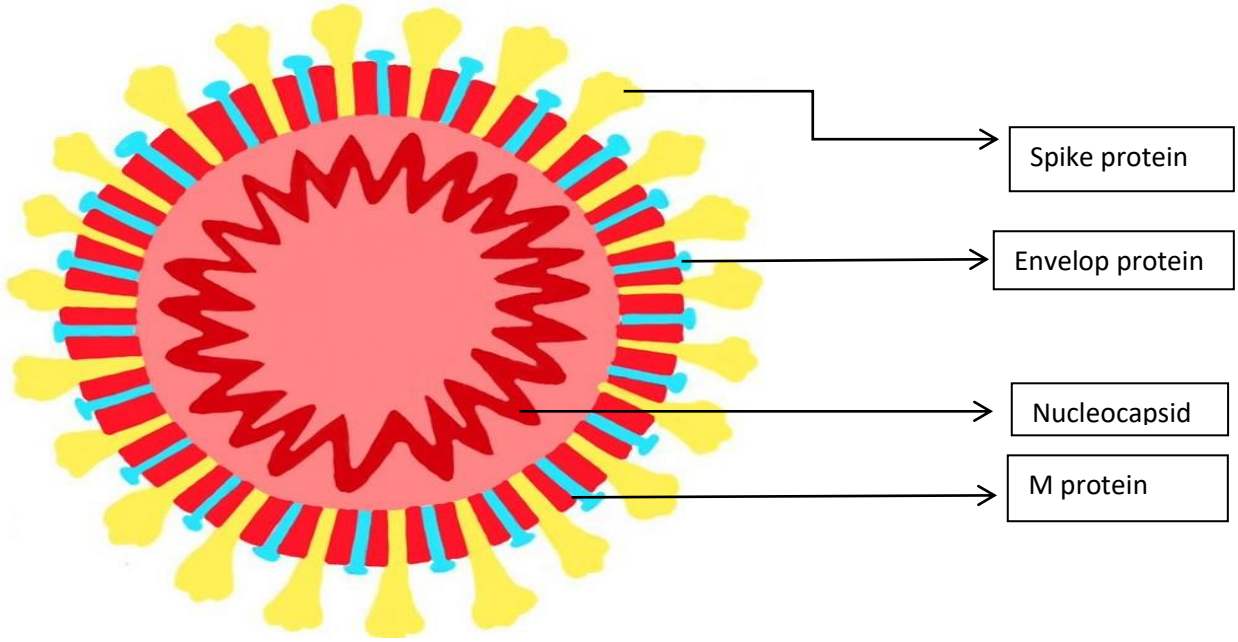
In the February it was identified that covid 19 was thought to transmit from person to person through respiratory droplets.

The WHO characterized covid 19 as '**PANDEMIC**" on March 112020.Later it was suggested that every person infected could infect 1.4 to 2.5 people and the exact reproduction number is unknown and advised for social distancing among people.

CHEMISTRY AND PATHOGENESIS:

At the Genomic levels 96% it is identical to bat corona viruses [2]The four major structural genes of corona viruses includes "the membrane glycoprotein(M),Spike protein (s), Nucleo capsid (N)and Envelope protein (E).[3] as shown in figure 2.

Figure 2: STRUCTURE OF SARS COV2.



Receptors:

The receptors for corona viruses are acetyl sialic acid (9-o-acetyl sia) receptors. The main receptor for SARS COV2 is (ACE2) Angiotens in converting Enzyme 2[4] which is seen mostly in TYPE I and TYPE II alveolar epithelial cells of lungs[5] .The receptor binding capacity of SARS COV2 is **10-20** times stronger than that of SARS- COV[6] .The drug targets are the RNA dependent polymerases and proteases.

PATHOGENESIS:

The envelope spike protein of SARS COV2 is divided into S1 and S2 domain.S1 is for receptor binding and S2 is for cell membrane fusion[7].The S1domain of SARS COV2 covers almost 50 amino acids[7].After the receptor binding the SARS COV2,enters the host cells, to inhibit the innate immune response. The exact mechanism is explained in the following sequence.

Mechanism of pathogenesis:

SARS COV2

⇩

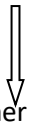
Enters the host cells by binding with ACE2 receptors

⇩

Inhibits or evades innate immune signalling

⇩

Expression of interferon stimulated genes by host to inhibit the viral replication



Excessive immune response together with the lytic effects of the virus results in pathogenesis of the disease.

COVID 19 Disease.

EFFECTS OF SARS COV2 ON VARIOUS SYSTEMS:

ORAL CAVITY:

The Gingival sulcus and salivary glands are the potential reservoirs of SARS COV2.

The Gingival sulcus releases various enzymes like flucosidase, mannosidase , hexosaminidase , sialidase... which modulates the respiratory surfaces and thereby increase the microbial colonies.[9]The Gingival microbes also causes loss of fibro nectin from respiratory and oral mucosa thereby increasing the microbial adherence[10].

The Gingival sulcus is a favourable site harbouring various pathogenic viruses including human herpes viruses, human papilloma virus...In such cases, the viruses modulate the local environment aiding their retention, which in turn triggers the reactivation of the viruses. The ACE2 receptors are also present in the epithelium of gingival and salivary glands[11,12].The SARSCOV2 mainly spreads through nasal discharge or from droplets of saliva.

SALIVA:

Saliva is present at the entry of the respiratory system which helps in early diagnosis and also promotes transmission of infectious diseases. Because of the non invasive nature and lesser health hazard to health care workers collection of salivary specimen has the advantages of patient acceptance and also provides more security for health professionals. The three most common modes of saliva collection includes saliva swabs, from salivary glands near the ducts, coughing out saliva[13].SARS-COV2 was detected from posterior oropharyngeal salivary samples with a high viral load during the presentation of the disease.[14,15]

Oral swabs from most of the patients tested positive for SARS COV2 and the positive results are shown at an early stage. So these may indicate early infection of SARS COV2.[16]Saliva may be collected from salivary ducts in order to prevent contamination from respiratory secretions.[17]Saliva collection by coughing out method is done in patients who were hospitalized and it is done after a few days of hospitalization.

All these specimen were tested for “s gene “using RT-PCR method. Live viruses were detected from some of the samples by virus culture.

In one of the studies it is shown that the temporal profile of viral load of saliva reached a peak of the viral load during the first week.[18]The tongue and the salivary gland expresses ACE2 receptors which suggests oral cavity as the host for SARS COV2 and its possible invasion into these tissues.ACE2 receptors were enriched in epithelial cells of the tongue, epithelial cells of T cells, B cells ,fibro blasts of the mucosa.

Some of the animal studies also showed the ACE2+ epithelial cells in salivary glands are the targeted host as early as 48 hrs after infection.[19]CO209L has also been added as another possible receptor.[20]

Furin cleaves the viral envelope glycoprotein thereby enhancing infection with host cells. A furin like cleavage site has been identified in the spike protein of SARS-COV2.The activation site of SARS COV2is activated by furin.[21]Expression of furin was detected by immunostaining in tongue epithelium.

The salivary droplets are generated by coughing, sneezing and talking. About three thousand salivary droplet nuclei could be generated in one cough and about 40,000 salivary droplets which reaches several meters can be generated by one sneeze. So SARS COV2 can be transmitted through saliva and saliva can also be taken as a diagnostic tool for early detection of the virus.[22,23]

CLINICAL MANIFESTATIONS:

The clinical findings of the oral cavity includes multiple pin point petechiae like ulcers which mimics recurrent herpes, Geographic tongue, dysguesia ,Xerostomia and gingivitis. Enanthems associated with skin lesions were classified into 4 categories: , macular, petechiae ,macular with petechiae, or erythemato vesicular. [24]

GASTROINTESTINAL SYSTEM:

Digestive symptoms other than respiratory symptoms is an alternate source of infection when people are in contact with infected individuals. The most common digestive symptoms include abdominal pain, nausea, vomiting ,diarrhoea and anorexia[25].The less common symptoms being anosmia, dysguesia. The receptors are mainly ACE2 and TMPRSS(Trans membrane seriene protease).[26]ACE2 receptors are highly expressed in upper oesophagus ,the cells of stratified squamous epithelium and absorptive enterocytes from ileum and colon. Due to increase in permeability of GI wall to foreign bodies once infected with the virus diarrhoea may occur due to the invaded enterocyte

mal absorption .[27] Changes in the composition ,function of the flora of the digestive tract affects respiratory tract through the common mucosal immune system, and the respiratory tract flora disorders in turn affects the digestive tract through immune regulation. This effect is called the “gut-lung axis”.[28,29] .Xu and colleagues found that there are some differences in the micro environment between adult and paediatric GIT systems.[30].There is also a possibility of fecal oral transmission. The viral nucleic acids of loose stools and the respiratory system both tested positive in patients with severe COV2.

LIVER TOXICITY:

The liver may also get affected because of the expression of ACE2 cells on liver. Patients with digestive symptoms had higher mean liver enzyme levels, lower monocyte count and longer prothrombin time..

RESPIRATORY SYSTEM:

The primary involvement of the disease is the respiratory system and the main mode of transmission is through respiratory droplets. The chest CT is often recommended for patients with covid 19.The initial chest CT findings includes bilateral multilobar Ground Glass Opacification mainly in the lower lobes and less frequently in the right middle lobe .The other less common findings includes pleural thickening, septal thickening and bronchiectasis, sub pleural involvement.[31]

Follow up CT showed increase in number and size of Ground glass Opacification which later transformed into multifocal consolidative opacities, septal thickening and crazy paving pattern. The severity of CT findings are greatest around the **10^{th} day** after the onset of symptoms.

"Acute Respiratory Distress Syndrome" is the main indication to transfer patients to emergency unit like Intensive Care Unit. Various authors have classified the chest CT findings of covid 19 pneumonia based on their symptoms.

.According to **Jin et al**[32].the CT findings are classified into many stages as Ultra early, early, rapid progression, consolidation and dissipation stages.

Ultra early Stage(asymptomatic patients 1-2 weeks after exposure):

CT showed single or multiple focal GGO and air bronchogram

Early stage(symptomatic presentation):

CT showed single or multiple GGOs or GGO combined with interlobular septal thickening.

Rapid progression stage: (days 3-7 of symptomatic presentation):

CT showed large light consolidative opacities and air bronchograms

Consolidation stage:(2^{nd} week of symptomatic presentation):

CT showed reduction in density and size of consolidative opacities.

Dissipation stage:

2-3 weeks after the onset CT may show dispersed patchy consolidation opacities, reticular opacities referred to" strip like opacities" bronchial wall thickening and interlobular septal thickening.

CARDIOVASCULAR SYSTEM:

Some of the patients with severe covid 19 experienced acute myocardial infarction and hyper coagulability. [33,34,35]

On Electrocardiography these patients showed ST segment elevation confirming the potential to get acute myocardial infarction.[36]

On Echocardiography they showed reduced left ventricular ejection fraction and regional wall motion abnormalities.[36]

Troponin T and D dimer were seen under lab investigations.[37]

The reasons for myocardial injury could be due to cytokine storm, hypoxic injury, coronary spasm, plaque rupture, micro thrombi, direct vascular or endothelial injury.[38]

CENTRAL NERVOUS SYSTEM:

Patients of severe covid 19 with "Acute Respiratory Distress syndrome" experienced ,diffuse corticospinal tract signs with tendon reflexes ,bilateral extensor plantar reflexes and ankle clonus [39].Some of the patient experienced large vessel stroke with cough, head ache, chills…[40]

A few of them had **dy sexecutive syndrome** which includes inattention ,disorientation, poorly organized movements in response to command.[41]

These patients were subjected to undergo MRI and Electron cephalography. The MRI findings includes bilateral fronto temporal hypo perfusion and lepto meningeal space enhancements. On electron cephalography only non specific changes were noted. Some patients had bi frontal slowing consistent with encephalopathy.[41]

STROKE:

Patients with Covid 19 also experienced large vessel stroke with the symptoms of cough, head ache and chills for a week which develops in a healthy individual. They later developed progressive dysarthria, with both numbness and weakness in one of the arms and legs. Other investigations like computed tomography and CT angiography showed partial infarction of the middle cerebral arteries and partially occlusive thrombus in the coronary artery at the level of bifurcation.

URINARY SYSTEM:(KIDNEYS):

The kidney cells have receptors similar to that of lung cells[42] and paves way for the entry of SARS COV2 and thereby the kidneys get infected. Sperati says patients with co existing chronic conditions like high BP and diabetes can increase the risk of kidney disease. It was suspected that people who did not have kidney problems before could have been infected with the virus. Patients with severe covid 19 had Acute Kidney Injury(AKI)i.e sudden loss of kidney function.[43]

The various possible reasons could be low levels of oxygen in the blood as a result of Pneumonia or may be a cytokine storm[44] and also tiny blood clots that are formed in the blood stream which can clog the smallest blood vessel in the kidney which impairs its function.

The signs of kidney problems in the patients with covid 19 include high levels of protein in urine and abnormal blood work.

Kidney damage arising in patients with severe covid19 is a " warning sign" of the fatality of the disease. Patients with Acute Kidney injury(AKI)who do not have to go for dialysis will have better recovery rate, than those who needs dialysis. Patients with high risk includes hypertensive ,those with kidney transplants and autoimmune diseases. Hypertension may lead to kidney failure[45] and hence these patients are advised to take their regular medication(including ACE inhibitors and Angiotens in receptor blockers. Patients with autoimmune diseases and kidney transplants need to

take immunosuppressive drugs and anti rejection medicines .In patients with kidney failure ,the disease course was more severe than in normal population. So precautions are mandate for those with high risk for renal damage.

EYES:

Generally corona viruses cause anterior uveitis ,retinitis, vasculitis and optic neuritis in eyes. Some of the early manifestations of SARS COV2 includes conjunctivitis also called as" pink eye or red eye" or any tear in the conjunctiva. "Chemosis" was seen in advanced cases and" epiphora" has also been reported in other cases.[46]

The possible reasons could be

*direct inoculation of the virus into the tissues

*aerosolized virus particles

*through nasolacrimal duct

*hematogenous spread through lacrimal glands.[47]

The eye infections are known to be contagious and the trans conjunctival aerosol infection is the possible mode of transmission.

The clinical evaluation is done by anterior segment examination at the slit lamp to confirm the findings of conjunctiva .The dilated fundus examination and the measurement of intra ocular pressure may also be warranted. The detection of SARS COV2 in eyes was done by obtaining conjunctival swab .The sample for detection of virus is collected by sweeping the lower eyelid fornices[48] to collect tears and conjunctival secretions with virus sampling swabs after the topical application of (1% amethocaine eye drops for example) and the samples are re processed by detecting two genes OR Fla band Nucleo capsid N. The lab findings include increased levels of WBC count, C- Reactive protein and high levels of prolactin and lactate de hydrogenase.

The treatment of SARS COV2 in eyes includes symptomatic relief, topical antibiotics, to prevent super infection.[49]The preservative free artificial tears, lubricating ophthalmic ointments and cold compresses has also been given for the patients. As this is self limiting in eyes the advanced treatment strategies are not required.

SKIN:

Skin rashes are the most prominent and most common symptoms of patients with severe covid 19.The rashes may be further classified into :

1. Hives type (Utricarial): Skin turns red ,seldom swelling occurs.
2. Prickly heat type(Chicken Pox type):present for many days.
3. Covid fingers and toes(Chilblains):reddish and purplish bumps on fingers and toes.

A covid piel study also concluded that there are five clinical patterns of skin lesions with the affected patients which includes :

1. Vesicular
2. Utricarial
3. Maculopapular
4. Pseudo chilblain
5. Livedo/Necrosis [50] .

Other studies has also concluded that 17% of the patients who tested positive for SARS COV2 showed skin rashes as their first symptom. One in five people who tested positive reported skin rashes as their symptoms.

Recalcati says that exanthematous lesions like Urticaria, chickenpox like lesions, purpuric and petechial changes ,transient livedo, reticularis and acroischemic lesions are common in both viral infections and adverse drug reactions. Enanthems (oral cavity lesions) distinguish between these two reactions. Oral cavities of patients presenting with skin reactions are examined. Pustular or dusky lesions indicates drug reactions whereas Vesicular/Petechial patterns along with enanthems indicates infectious etiology.

Skin problems like pressure injury, contact dermatitis, seborrhic dermatitis ,acne may also arise as a result of prolonged skin contact with personal protection equipment and excessive personal hygiene. Care should be taken for patients with autoimmune diseases and chronic inflammatory disorders such as psoriasis , atopic dermatitis ,Lupus erythematosus , sialadenitis, suppurativa.

CONCLUSION:

The risk factors includes old age, cardiovascular disease, chronic lung disease, hypertension ,diabetes and obesity. The lab findings of patients with poor outcomes includes increase in levels of D dimer , Troponin, increased prothromb in time ,increase in liver enzymes ,C reactive protein and ferritin. The Older treatment modalities of severe covid included Plasma therapy(injection of plasma antibodies from affected individuals)and antiviral therapy (remdesivir) and steroids to prevent lung inflammation and fibrosis. Supportive oxygen therapy is mandatory for persons with severe lung infection. After conducting many clinical trials Vaccines are now available in European, Asian and American countries. One of the current treatment modalities includes Vaccination. Even though Vaccines are available newer mutant strains are still making the Pandemic worse. Prevention is always better than cure. Face masks, proper hand washing and maintaining social distancing helps in preventing the spread of the disease. People with Co morbidities should take their regular medication to avoid serious illnesses.

Funding Acknowledgement: This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Conflict of interest statement: The authors declare no conflict of interest in preparing this article.

ETHICS: No ethical permission is required.

CONSENT: Since this is collection of data for review article no consent is needed.

REFERENCES:

1.HarapanHarapan[abc]NaoyaItoh[d]AmandaYufika[e]WiraWinardi[f]SynatKeam[g]HayphengTeMudatsirMudatsir et al.Corona virus disease 2019 (COVID-19): A literature review Journal of Infection and Public Health 13 (2020) 667–673.

2.Kramer A, Schwebke I, Kampf G. How long do noso comial pathogens persist on inanimate surfaces? A systematic review. BMC Infect Dis 2006;6:130.

3.Danish Rafiq1 | Asiya Batool2 | M. A. Bazaz1Three months of COVID-19: A systematic review and meta-analysis.RevMedVirol.2020;30:e2113.

4.Zhou P, Yang XL, Wang XG, et al. A pneumonia outbreak associated with a new corona virus of probable bat origin. Nature. 2020;579:270- 273. https://doi.org/10.1038/s41586-020-2012-7.

5. Zhang H, Penninger JM, Li Y, Zhong N, Slutsky AS. Angiotensin converting enzyme 2 (ACE2) as a SARS-CoV-2 receptor: molecular mechanisms and potential therapeutic target. Intensive Care Med. 2020;3:1-5. 14.

6.Hamming I, Timens W, Bulthuis ML, Lely AT, Navis GJ, van Goor H. Tissue distribution of ACE2 protein, the functional receptor for SARS corona virus. A first step in understanding SARS pathogenesis. J Pathol. 2004;203(2):631-637. 15.

7. Wrapp D, Wang N, Corbett KS, et al. Cryo-EM structure of the 2019-nCoV spike in the prefusion conformation. Science. 2020;367 (6483):1260-1263.

8. Lu R, Zhao X, Li J, Niu P, Yang B, Wu H, et al. Genomic characterization and epidemiology of 2019 novel corona virus: implications for virus origins and receptor binding. Lancet 2020.

9.Gomes-Filho IS, Passos JS. Da Cruz SS. Respiratory disease and the role of oral bacteria. J Oral Micro biol 2010;2..https://doi.org/10.3402/jom.v2i0.5811.

10.Wikström M, Linde A. Ability of oral bacteria to degrade fibronectin. Infect Immun 1986;51:707.

11. Xu J, Li Y, Gan F, Du Y, Yao Y. Salivary Glands: Potential Reservoirs for COVID-19 Asymptomatic Infection. J Dent Res 2020.

12.Santos CF, Akashi AE, Dionísio TJ, Sipert CR, Didier DN, Greene AS, et al Characterization of a Local Rennin-Angiotensin System in Rat Gingival Tissue. J Periodontol 2009;80:130–9.

13.Ruoshi Xu1 , Bomiao Cui2 , Xiaobo Duan 1 , Ping Zhang2 , Xuedong Zhou2 and Quan Yuan Saliva: potential diagnostic value and transmission of 2019- nCoV International Journal of Oral Science.

14. To KK, Tsang OT, Leung WS, Tam AR, Wu TC, Lung DC, et al. Temporal profiles of viral load in posterior oropharyngeal saliva samples and serum antibody responses during infection by SARS-CoV-2:

15. To, K. K. et al. Consistent detection of 2019 novel coronavirus in saliva. Clin. Infect. Dis2020

16.Zhang, W. et al. Molecular and serological investigation of 2019-nCoV infected patients: Implication of multiple shedding routes; Emerg. Microbes .Infect.

.386–389 (2020).

17. Chen, L. et al. Detection of 2019-nCoV in Saliva and Characterization of Oral Symptoms in COVID-19 Patients.(2020).

18 .To, K. K.-W. et al. Temporal profiles of viral load in posterior oropharyngeal saliva samples and serum antibody responses during infection by SARS-CoV-2: an

observational cohort study. Lancet Infect. Dis. (2020).

19 . Liu, L. et al. Epithelial cells lining salivary gland ducts are early target cells of

severe acute respiratory syndrome corona virus infection in the upper respiratory

tracts of rhesus macaques. J. Virol. 85, 4025–4030 (2011).

20.Divya Vinayachandran a , Saravanakarthikeyan, Balasubramanian b*Salivary diagnostics in COVID-19: Future research implications Journal of dental sciences(2020) 15 264-266.

21.smriti M. Why does the corona virus spread so easily between people. Nature 2020;579:7798

.22.Kohn, W. G. et al. Guidelines for infection control in dental health-care settings-

2003. MMWR Recomm. Rep. 52, 1–61 (2003).

23. Cole, E. C. & Cook, C. E. Characterization of infectious aerosols in health care facilities: an aid to effective engineering controls and preventive strategies. Am. J. Infect. Control 26, 453–464 (1998)

24. Drago F, Paolino S, Rebora A, et al. The challenge of diagnosing atypical exanthems: a clinico-laboratory study. J Am Acad Dermatol. 2012;67(6):1282-1288.

25.Brandon Michael Henry1 · Maria Helena Santos de Oliveira2 · Justin Benoit3 · Giuseppe Lippi4Gastrointestinal symptoms associated with severity of corona virus disease 2019 (COVID-19): a pooled analysis Internal and Emergency Medicine .

26.Huang Q, Herrmann A. Fast assessment of human receptor-binding capability of 2019 novel corona virus (COVID-19). Preprint. Posted online February 04, 2020.

27. Jin yang Gu Bing Han Jian Wang COVID-19: Gastrointestinal Manifestations and Potential Fecal–Oral Transmission Gastroenterology 2020;158:1518–1519

28. Budden KF, Gellatly SL, Wood DL, et al. Emerging pathogenic links between micro biota and the gut-lung axis. Nat Rev Microbiol 2017;15:55–63.

29. 29. He Y, Wen Q, Yao F, et al. Gut-lung axis: The microbial contributions and clinical implications. Crit Rev Micro biol 2017;43:81–95.

30..Xu Y, Li X, Zhu B, et al. Characteristics of pediatric SARS-CoV-2 infection and potential evidence for persistent fecal viral shedding. Nat Med 2020; 26: 502–05.

31.Sana Salehi1 Aidin Abedi Sudheer Balakrishnan Ali Gholamrezanez had, Corona virus Disease 2019 (COVID-19): A Systematic Review of Imaging Findings in 919 PatientsAJR:215, July 2020

32. Jin YH, Cai L, Cheng ZS, et al.; Zhongnan Hospital of Wuhan University Novel Corona virus Management and Research Team; Evidence-Based Medicine Chapter of China International Exchange and Promotive Association for Medical and Health Care (CPAM). A rapid advice guideline for the diagnosis and treatment of 2019 novel corona virus (2019-nCoV) infected pneumonia (standard version). Mil Med Res 2020; 7:4.

33.. Clerkin KJ, Fried JA, Raikhelkar J, et al. Corona virus Disease 2019 (COVID-19) and cardiovascular disease. Circulation 2020 March 21 (Epub ahead of print).

34. Xie Y, Wang X, Yang P, Zhang S. COVID-19 complicated by acute pulmonary embolism. Radiology: Cardiothoracic Imaging. 2020;2(2):e200067.

35. Danzi GB, Loffi M, Galeazzi G, Gherbesi E. Acute pulmonary embolism and COVID-19 pneumonia: a random association? Eur Heart J 2020 March 30 (Epub ahead of print).

36.Sripal Bangalore, M.D., M.H.A. Atul Sharma, M.D. Alexander Slotwiner, M.D. New York University Gross man School of Medicine New York, NYST-Segment Elevation in Patients with Covid-19 — :A Case series. The New England journal of medicine.

37.Choi S, Jang WJ, Song YB, et al. D-dimer levels predict myocardial injury in ST-segment elevation myocardial infarction: a cardiac magnetic resonance imaging study. PLoS One 2016; 11(8):e0160955.

38. Tavazzi G, Pellegrini C, Maurelli M, et al. Myocardial localization of corona virus in COVID-19 cardio genic shock. Eur J Heart Fail 2020 April 10 (Epub ahead of print).

39.Julie Helms, M.D., Ph.D. Stéphane Kremer, M.D., Ph.D. Hamid Merdji, M.D.et al Neurologic Features in Severe SARS-CoV-2 Infection ,The New England Journal o f Medicine

40.Thomas J. Oxley, M.D. J. Mocco, M.D. Shahram Majidi, M.D. Christopher P. Kellner, M.D. Hazem Shoirah, M.D. I. Paul Singh, M.D. Reade et al Large-Vessel Stroke as a Presenting Feature of Covid-19 in the Young . n engl j med nejm.org.2020

s41.Julie Helms, M.D., Ph.D. Stéphane Kremer, M.D., Ph.D. Hamid Merdji, M.D. Raphaël Clere-Jehl, M.D. Malika Schenck, M.D. Christine Kummerlen, M.D. Olivier Collange, M.D., Ph.D.et al. Neurologic Features in Severe SARS-CoV-2 Infection. N Engl J Med.2020 Apr 15 : NEJMc2008597.

42.Qi-Lin Chena Jia-Qi Lib Zhi-Dan Xianga Yue Langa Guo-Ji Guob Zhi-Hong Liua , Localization of Cell Receptor-Related Genes of SARS-CoV-2 in the Kidney through Single-Cell Transcriptome Analysis. Kidney Dis 2020;6:258–270.

43.Lili Chan,1,2,3,4 Kumardeep Chaudhary,3,4,5 Aparna Saha,3,4 Kinsuk Chauhan , 1 Akhil Vaid,6 Shan Zhao,6,7 Ishan Paranjpe,6et al AKI in Hospitalized Patients with COVID-19.JASN 31: ccc–ccc, .2020.

44.Al-Lamki R, Wang J, Vandenabeele P, Bradley J, Thiru S, Luo D, et al. TNFR1-and TNFR2-mediated signaling pathways in human kidney are cell type-specific and differentially contribute to renal injury. FASEB J. 2005;19:1637-45. doi: 10.1096/fj.05-3841com.

45.Elaine Ku, Benjamin J. Lee, Jenny Wei, and Matthew R. Weir Hypertension in CKD: Core Curriculum 2019Am J Kidney Dis. 74(1): 120-131. Published online March 19, 2019.

46.Wu P, Duan F, Luo C, Liu Q, Qu X, Liang L, Wu K. Characteristics of Ocular Findings of Patients With Corona virus Disease 2019 (COVID-19) in Hubei Province, China. JAMA Ophthalmol. 2020 May 01;138(5):575-578.

47.Seah I, Agrawal R. Can the Corona virus Disease 2019 (COVID-19) Affect the Eyes? A Review of Corona viruses and Ocular Implications in .Humans and Animals. Ocul Immunol Inflamm. 2020 Apr 02;28(3):391-395.

48.Xia J, Tong J, Liu M, Shen Y, Guo D. Evaluation of corona virus in tears and conjunctival secretions of patients with SARS-CoV-2 infection. J Med Virol. 2020 Jun;92(6):589-594.

49.Varu DM, Rhee MK, Akpek EK, Amescua G, Farid M, Garcia-Ferrer FJ, Lin A, Musch DC, Mah FS, Dunn SP., American Academy of Ophthalmology Preferred Practice Pattern Cornea and External Disease Panel. Conjunctivitis Preferred Practice Pattern®. Ophthalmology. 2019 Jan;126(1):P94-P169.

50 .C.Galván Casas A.Català G.Carretero Hernández P.Rodríguez-Jiménez D.Fernández-Niet et al . Classification of the cutaneous manifestations of COVID-19: a rapid prospective nation wide consensus study in Spain with 375 cases.British Journal of Dermatology (2020) 183, pp71–77.