Review on Automated COVID-19 Detection Using Deep Learning

Amanpreet Singh, Department of Electronics and Communication Engineering
Punjabi University, Patiala, Punjab, India, asodhi.pta@gmail.com
Dr. Charanjit Singh, Assistant Professor, Department of Electronics and Communication Engineering, Punjabi University, Patiala, Punjab, India, channisingh@yahoo.com

Abstract- The new improvements in machine learning algorithms support the classification and identification of various lung problems in medical images. Consequently, lot of work on the discovery of lung infections using machine learning can be found in this writing. This paper gives a review for COVID-19 lung infection identification in medical images using deep learning. There have been very few research contribution till now in regard to this. The main objective of this review is to introduce a scientific classification of the cutting edge deep learning based COVID-19 identification system, envision the pattern of recent work in this field and recognize the leftover problems and likely future headings in this field. The classification comprises of different sections that are studied in articles: types of images, features, information expansion, and sorts of deep learning algorithms. The introduced method could be utilized by different analysts to design their exploration commitments and exercises. The proposed technique could additionally work on the productivity and increment the quantity of deep learning supported lung illness discovery applications.

Keywords* — *Deep Learning, Medical Images, COVID-19 Detection, X-Ray Images, Machine Learning.

I. Introduction

The flare-up of COVID-19 continues to affect public wellbeing and worldwide prosperity. Firstly, in December 2018 this infection was perceived in a city named Wuhan located in China, and on March 11, 2020 WHO (world health organization) declared this as pandemic [1]. Over 27 crore people have been impacted with COVID-19 all around the world, within excess of 5,345,727 misfortunes of life [2]. The transmission rate of COVID19 is found terrifying in studies, it is found between 2.24-3.58 that is on much higher level than any other kind of infection viral. [3]. Early determination and separation of potentially irresistible cases is a huge advancement in battle against COVID-19. The highest quality level evaluating approach for distinguishing the COVID is RT-PCR (reverse transcription polymerase chain reaction) with the help of respiratory samples [4]. In any case, this determination practice has a deficiency of testing units, lacking research centres, much time consuming and low affectability that shows contemporary general wellbeing crises, numerous patients won't distinguish immediately [5]. Along these lines, it will additionally foster the danger of contaminating a sound local area. Thus, medical professionals have found an elective screening technique that is quick and more delicate like Chest X-ray or CT-Scans that shows the visual markers associated with this viral contamination [6]. Investigations have discovered that patients, deformations in chest X-rays assuming they are impacted with Coronavirus. The scanning equipment's are viewed as a fast evaluating device for the quick recognizable proof of infected individuals in the scourge region. An extensive disadvantage of CT scanning is that in numerous immature and emerging nations, imaging equipment's are not generally accessible.

As a rule, if a patient has symptoms of infection, such as a cough, fever or breathing problem, doctors decide to go for a chest X-Ray. A very uncommon observation is the "ground-glass opacities", which shows that part of the lungs take on a dark gray color as opposed to being black with positive white markings on the veins. Lungs of patients with primary COVID-19, shows diffuse or multifocal solidification, which appear to be "white lungs". CXR, however, is not overly sensitive in mild to moderate in patients, and has been found to be more prevalent in different types of Covid, like major respiratory disorders (SARS) and respiratory infections (MERS) [7, 8].

Most medical clinics around the globe have CXR machines or standard radiography units by which we can obtain 2D (2-Dimensional) chest images of patients. However, the need for professional radiologists and the extensive opportunity for CXR surgery is a fundamental test during this epidemic. Next, promote a computer-assisted diagnostic system (CAD) to help a specialist to check infection in a productive and accurate way. The introduction of a CAD

 DOI : 10.35291/2454-9150.2022.0025

strategy totally depends on the presentation of images (or features). In order to obtain a dignified representation of the photographic information, a great deal of effort is required in the pre-processing of the image and in the translation, which is disturbing and includes the inability to read the text. Ideally, an deep learning approach (DL) can advance the preparation cycle in such a way by removing various aspects of the level image without any human interference. If we check for the last few years, deep learning models performed quite well in a variety of clinical imaging modalities, for example, breast cancer [9], cervical and lung cancer [10, 11], integration of lung knobs [12], and getting better results over other AI models. Essential tests to find a functional CAD framework are not only due to the lower contrast images in addition to the soft tissue coverage of the chest ribs but moreover it is lacking in defined data. A deep learning strategy requires multiple data sets to achieve dramatic execution [13].

Fang et al. proposed a review of the interaction of viral nucleic acid detection and CT scan of chest strategy using RT-PCR to detect COVID-19 cases [14]. The 51 subjects who had a history of movement or residence in Wuhan, china for at least 14 days and who had any symptoms like fever or respiratory effects, aged 45, are taken part of this survey. 36 patients were tested with infection in a baseline RT-PCR trial. 12 of them achieved good results in second RT-PCR test (1-2 days). 2 patients were tested for infection in the third RT-PCR trial (2-5 Days) and 1 patent take 4 tests (7 Days). From this study, 98% of total 51 patients showed proof of pneumonia on the first day. As a result, findings of this review found that the accuracy of chest CT was much higher than higher than RT-PCR (98% compared to 71%, respectively). The general bock diagram of covid-19 detection is shown in the Fig 1 below.

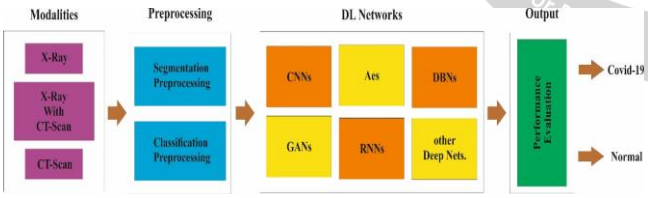

Fig 1: General Diagram of COVID-19 detection

II. MAIN INFECTED ORGANS DUE TO COVID-19

Covid spares no significant organ in the body. For certain patients, the infection spreads its deadly arms to numerous organs. In the infection isn't recognized in the underlying stage, it attacks the lower respiratory lot. Although the vast majority of the patients foster extreme respiratory issues, different Organs such as the brain, nerves, heart, stomach, liver and kidneys are also affected. The main affected organs due to Covid-19 has been shown in the Fig 2.

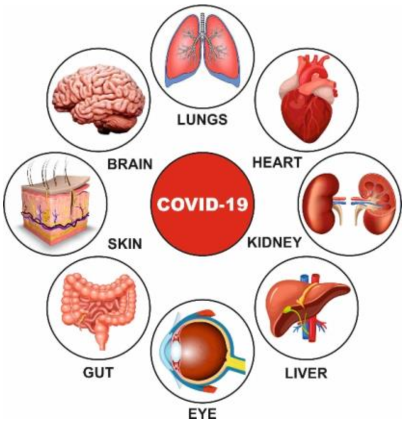

Fig 2: Infected organs due to COVID-19

A. Lungs

There is an impressive debate over the air distribution of SARS-CoV-2 without strong evidence. One report recommends vaporizer infection lasting 3 hours [16]. As a result of the high exposure of ACE2 to these cells, the epithelial cells that line with the throat fill up as a defence against infection. These cells cause the infection to continue and, if not killed by antibodies, are released in large quantities, indicating that they can spread to others. The next target is lung infection, and it contains ACE2 receptors. Type-II pneumocystis plays a significant role in the formation of alveolar surfactant, which decreases the pressure on the alveoli and airways and allows for O2 / CO2 exchange and it also prevents their breakage [17]. The mutation component of these cells affects their related cycles and specific physiology, showing lung inflammation. At that point, the cells capture the infection / protein as unknown antigens and lymphocytes begin to produce immunoglobulin M (IgM), IgA, and IgG [18]. 5% of patients with Covid-19 have a real serious pneumonia, and multiple organ damage and a cytokine storm may be a possible explanation for that view. The exaggerated immune response causes dead cells and fluids to settle, blocking the airways and alveoli, thereby preventing O2/CO2 conversion and the development of pneumonia. CT scans and Chest X-Rays highlight white light in areas where dark spots (air) are found is due to closure of the alveoli by WBCs, fluids and lung cells which are dead [19].

B. Heart and Veins

ACE2 receptor have other focus areas that are heart and nerves, leading to SARS-CoV-2. Among 416 patients at Renmin Hospital, Wuhan, 19.7% had serious heart attacks and were at risk for congestive heart failure [20]. One report elevated arrhythmia in 16 out of 36 ICU patients at Zhongnan Hospital, Wuhan. The infected people receive antiviral treatment (no specific drug prescribed), and antiviral drugs such as hydroxylchloroquine are known to cause arrhythmia [21]. Myocarditis due to soreness of the myocardium has also been identified. Antiviral drugs are at the highest risk for heart disease and may indicate heart

 DOI : 10.35291/2454-9150.2022.0025

failure, damage, and mood swings. Rabwairin, which is used medically, is thought to be the first cause of a chronic sinus infection. In addition to these methods, it is important that you carefully monitor and pay special attention to the cardiovascular system in patients suffering with COVID-19. Another review of 184 obese patients it is found that 31% were facing thrombotic complications at very high level, and that venous and vascular thromboembolism due to high soreness was a major risk factor [22]. Blood lumps reach the lungs, brain, and heart are a major risk factor for pneumonic embolism and heart failure, thromboembolism at various levels. Kawasaki disease is found in youngsters aged 4-11 years infected with SARS-CoV-2 [23]. At 6 months the Covid-19 patient had bulbar conjunctivitis, erythema, and edema with fever and maculopapular rash manifesting in upper extremities. Respirational symptoms such as coughing, constipation, or rhinorrhea are common. The Broken Kawasaki is a 5-year example of a remedy. It is important to examine the clinical course of pediatric patients with COVID-19 associated with Kawasaki illness.

C. Kidneys

ACE2 receptors are also present in the glomeruli and proximal tubules in Kidneys that make them another target of infection. Covid-19 patients face signs like proteinuria, haematuria, and a surge in urea nitrogen and blood creatinine. Proximal tubules trap plasma proteins, and damage to these tubes increases protein retention in urine [24]. Haematuria may be initiated by glomerular obstruction. Though, haematuria and proteinuria are classified as widespread findings and require further examination to reveal details about their symptoms. SARS-CoV-2 RNA was spotted in urine tests obtained by RT-PCR and totally integrated infection was detected by transmission electron microscopy [25]. Electron microscopy also reveals the occurrence of viral cells in nearby tubes. Histopathological examination of the kidneys of 26 patients who died at Tongji Medical College in China revealed SARS-CoV-2 groups with podocyte and circular epithelium and severe proximal tubular injury. In critically ill patients, the primary immune response, cytokine storm, direct viral infection, and other hemodynamic factors may cause AKI to cause death in several patients due to kidney failure.

D. Liver

Liver damage is indicated by Aspartate aminotransferase (AST) and abnormal alanine transaminase (ALT) levels. Liver harm has been detected in approximately 15–53% of c cases with increased bilirubin, AST, and ALT [27]. Microvascular steatosis, Serious lobular and portal damage were detected in liver biopsies in outdated patients with infection. Side-effects of antimicrobials like hydroxychloroquine, which can cause severe hepatitis [28] and cytokine reuptake, can cause liver damage in critically ill patients.

E. Eyes

Conjunctivitis is also considered a clinical presence of disease and tears and in such cases, conjunctival fluid has been found to be effective in infection. A Chinese specialist who was diagnosed with the infection developed conjunctivitis before showing respiratory signs and was diagnosed with a viral fluid [29]. Other visible symptoms include epiphora, chemosis, prolonged ejaculation and conjunctival hyperemia. A review was conducted in Wuhan in which patients revealed that 27% of patients faced side effects afore the onset of respiratory indicators. It is recommended that visual acuity be mutual in people suffering with Covid-19 and observed during diagnosis [30]. Prolonged use of antimicrobials such as chloroquine and hydroxychloroquine is worrying as it can cause retina toxicity and retinopathy.

F. Gut

Sun Yat-sen University Hospital report from China reveled that of the 95 patients who had COVID-19, 58 cases of gastrointestinal manifestations (GI) [31]. The main side effects are in patients with anorexia, diarrhea and nausea, and are taken in a patient with severe throat and ulcer disease. Though, the association of ulcer and esophageal drainage with virus contamination is still unclear and is a dynamic review. It has been observed that the tissues of the abdomen, throat, duodenum, and rectum are more susceptible to infection, suggesting that these body part may also act as a straight mechanism of spread [31]. ACE2 receptors penetrate deep into the small intestine, colon, and stomach, causing unique damage to the SARS-CoV-2 digestive tract. Endoscopy revealed severe colon damage with hemorrhagic colitis and some patients were diagnosed with fecal viral RNA [32, 33]. In any case, there is no proof that the virus was spread through feces. The sound gut microbiota is essential for the proper working of the intestines. Microbial dysbiosis has been detected in patients with infection with a significant influence on Bifidobacterium sp. And Lactobacillus sp. It is a good idea to see if probiotic antibiotics can be used as a treatment to control GI infections caused by infection. However, we know very little about the use of probiotics against diseases and we can get more information by focusing on this area.

G. Skin

Skin, hands, and toes has also shown the other clinical signs a couple of weeks after virus infection. In one review, six Spanish patients with similar symptoms were diagnosed two weeks ago. Various injuries have been seen in the legs, soles and heels [34]. In different review, a 32-year-old lady from Ramon y Kajal Hospital in Madrid, Spain had an outbreak within 6 days of the onset of COVID-19 side

 DOI : 10.35291/2454-9150.2022.0025

effects. She was treated with azithromycin and hydroxychloroquine. Some isolated patients experience maculopopular eruption. A national study on skin symptoms throughout France has identified other skin types in patients with COVID-19. Symptoms include burns, cold urticaria, and vesicles such as chicken pox, exanthema, varicose veins, necrotic and non-necrotic purpura, chilblain ulcers, and broken cherry angiomas. [35] There have been isolated intelligences recommending skin exposure in infected patients. In any case, these are just warning reports and should continue to be investigated in order to link these predictions with SARS-CoV-2 disease.

H.Brain

A proper analysis of 214 patients from three specialized medical facilities at union hospital, wuhan showed that 36.04% of people with the virus had signs [36]. Side effects vary widely and range from severe cerebrovascular disease to epilepsy, ataxia, consciousness, prognosis, migraine and skeletal muscle damage. Loss of taste and smell and optical impairment are also the result of infections in the nervous system [36]. The nervous system is rich in ACE2, which makes them another target for the virus. Although breath shortness due to lack of oxygen is one of the most serious side effects of the disease, although blood oxygen levels are basically low, sometimes no such symptom is observed. The brainstem reflex helps to detect oxygen malnourishment [37] and absence of this may be a potential clarification for such a signal. It is important to check the levels of oxygen in any patient of this infection, as some patients have mild symptoms, but oxygen levels are quite basic. Brainstem fractures also cause altered relaxation cycles and jeopardize the independent regulation of the immune system, blood circulation, stomach, and respiratory systems [38]. However, further research and postmortem are needed to link the presence of a specific nervous system with viral infection.

III. TREATMENT OF COVID19 DISEASE

To date, powerful antibodies and promising antiretroviral drugs for this disease have not been developed and the drugs presently accessible are still being studied. So, many cases are being cured with anonymous medications. Many antidepressants are based on well-thought-out theory. Clinical level of COVID sites ranging from asymptomatic transport or moderate respiratory disease to severe pneumonia. Because no specific treatment for the infection is available, the proposed treatment is based on earlier SARS or Middle East Respiratory Syndrome (MERS) Covid experience. Many of the medicines currently used in this infection are antiviral specialists or support the immune system against COVID-19. Prior to the discovery of COVID-19 antimicrobial drugs, current treatment options were given to regenerative drugs. In this survey, we aim to demonstrate effective support strategies from a clinical perspective based on the latest clinical bits of evidence.

A. Remdesivir

Remdesivir, is a monophosphate product and an RNA polymerase inhibitor that utilizes C-adenosine nucleoside triphosphate that is effective against RNA infections, for example, coronavirus and Flaviviridae [39]. A substrate for RNA structures is Triphosphate-Type Remdesivir under RNA polymerase in Covid and viral RNA compounds. Each shows excellent in vitro movements fighting with certain Covids including SARS-CoV-2 with EC50 and EC90 rising 0.77 and 1.76 M respectively. Remdesivir is measured a potential treatment for COVID-19 at the onset of the epidemic.

B. Favipiravir

Another RNA polymerase inhibitor is Favipiravir a purine nucleotide product that inhibits viral repetition [40], and has been shown to be effective against SARSCoV-2 with a great EC50 of 61.88 M / L [41]. Different dosage rules have been proposed depending on the type of contamination [40]; 2,400–3,000 mg (two doses) of stacking component is considered for every 12 hours for COVID-19 treatment, while 1,200–1800 mg every 12 hours [42,40] lags behind the maintenance component. Favipiravir exhibits a good safety profile until the whole and true contrary effects and other drugs are used for temporary action.

C.Lopinavir

Lopinavir, an aspartate protease inhibitor for human immunodeficiency infection, has long been used to treat HIV infection. Ritonavir increases lobinavir fullness by pressing cytochrome P450. Protease inhibits 3CLpro activity through C2-symmetric packet in Lopinavir, which is not COVID [43]. Also, the inhibitory effect of lobinavir on virus is uncertain.

D.Chloroquine and hydroxychloroquine

Chloroquine is being used medicinally from over 70 years. It's the enemy who supports the malaria medicine; It is also being used for auto-immune diseases. Different studies have shown that it has an amazing ability to regulate infection in endothelial cells and transit stages [41]. The anti-bacterial components of chloroquine are different. It can inhibit nanoparticle synthesis by macrophages by simultaneously blocking the flow of clathrin-inhibited phosphatidylinositol to protein and subsequent clathrin-mediated endocytosis. In addition, chloroquine inhibits the fermentation of lysosomes, inhibiting their interaction with endocytic vessels in these lines [44].

A small lead with a randomized open label in France includes 36 patients with virus [45]. The viral load was completely reduced in 20 cases when treated with 200 mg

 DOI : 10.35291/2454-9150.2022.0025

hydroxychloroquine sulfate which was provided three times a day for 10 days after 6 days without treatment (70.0% vs 12.5%, P = 0.0001).

E. Traditional Chinese medicine

In the starting phase in China, no medications supporting the conduct of infection were banned. Thus, China's authorized law prescribes traditional Chinese medicine (TCM) with a mixture of antimicrobial medicines for patients with COVID-19. In China, TCM wards are located in medical clinics and some COVID-19 cases have been properly resolved. It is noteworthy that the authorities based on the actual clinical practice convened by Chinese law law refer specifically to the Qingfei Great Decoction (QPD) for cases verified by various categories. QPD contains 21 traditional Chinese instructions that are believed to have defensive effects on various body parts, including the lungs.

IV. CONCLUSION

Coronavirus is a growing pandemic that, in the short term, poses a serious threat to living across the globe. It directly upsets the lung cells and can cause irreparable damage, including death, if not diagnosed quickly enough. We have seen in this paper that infection can be precisely found by using X-ray or CT scan images. A comprehensive audit of improved detection of coronavirus analysis using the DL Network was conducted in this review. We have seen that one of the difficulties in building an accurate and robust detection system for Covid-19 is access to extensive public data sets. With more open data sets, we strongly believe that analysts can develop better DL models to more accurately predict COVID-19. As a result, it helps to develop a better performance model. We hope the information combination models will help in working on decision and assessment performance. Different features from the machine learning and deep learning models can be combined to construct precise models. In addition, efforts are underway to develop accurate segregation models as they contain images of the lungs by specialists. Having a definite reality is another challenge.

REFERENCES

[1] Novel Coronavirus – China, World Health Organization, 2020. https://www.who.int/csr/don/12-january-2020-novel coronavirus-china/en/.

[2] covid-19 coronavirus pandemic live data available at https://www.worldometers.info/coronavirus/ (Accessed Dec 15 2021)

[3] S. Zhao, Q. Lin, J. Ran, S.S. Musa, G. Yang, W. Wang, Y. Lou, D. Gao, L. Yang, D. He, et al., "Preliminary estimation of the basic reproduction number of novel coronavirus (2019-nCoV) in China, from 2019 to 2020 A data-driven analysis in the early phase of the outbreak", International Journal of Infectious Diseases 92 (2020), 214–217.

[4] P.J. Littrup, L. Freeman-Gibb, A. Andea, M. White, K.C. Amerikia, D. Bouwman, T. Harb and W. Sakr, "Cryotherapy for breast fibroadenomas", Radiology 234(1) (2005), 63–72.

[5] P. Huang, T. Liu, L. Huang, H. Liu, M. Lei, W. Xu, X. Hu, J. Chen and B. Liu, "Use of chest CT in combination with negative RT-PCR assay for the 2019 novel coronavirus but high clinical suspicion", Radiology 295(1) (2020), 22–23.

[6] Y. Li and L. Xia, "Coronavirus disease 2019 (COVID-19): role of chest CT in diagnosis and management", American Journal of Roentgenology (2020), 1–7.

[7] T.J. Franks, P.Y. Chong, P. Chui, J.R. Galvin, R.M. Lourens, A.H. Reid, E. Selbs, C.P.L. Mcevoy, C.D.L. Hayden, J. Fukuoka, et al., "Lung pathology of severe acute respiratory syndrome (SARS): a study of 8 autopsy cases from Singapore", Human Pathology 34(8) (2003), 743–748.

[8] A.E. Ahmed, H. Al-Jahdali, A.N. Alshukairi, M. Alaqeel, S.S. Siddiq, H. Alsaab, E.A. Sakr, H.A. Alyahya, M.M. Alandonisi, A.T. Subedar, et al., "Early identification of pneumonia patients at increased risk of Middle East respiratory syndrome coronavirus infection in Saudi Arabia", International Journal of Infectious Diseases 70 (2018), 51–56.

[9] D. Wang, A. Khosla, R. Gargeya, H. Irshad and A.H. Beck, "Deep learning for identifying metastatic breast cancer", arXiv preprint arXiv:1606.05718 (2016).

[10] H.-I. Suk and D. Shen, "Deep learning-based feature representation for AD/MCI classification, in: International Conference on Medical Image Computing and Computer-Assisted Intervention", Springer, (2013), pp. 583–590.

[11] S. Liu, S. Liu, W. Cai, S. Pujol, R. Kikinis and D. Feng, "Early diagnosis of Alzheimer's disease with deep learning", in: 2014 IEEE 11th international symposium on biomedical imaging (ISBI), IEEE, (2014), pp. 1015–1018.

[12] J.-Z. Cheng, D. Ni, Y.-H. Chou, J. Qin, C.-M. Tiu, Y.-C. Chang, C.-S. Huang, D. Shen and C.-M. Chen, "Computer-aided diagnosis with deep learning architecture: applications to breast lesions in US images and pulmonary nodules in CT scans", Scientific Reports 6(1) (2016), 1–13.

[13] M.M. Rahaman, C. Li, X.Wu, Y. Yao, Z. Hu, T. Jiang, X. Li and S. Qi, "A Survey for Cervical Cytopathology Image Analysis Using Deep Learning", IEEE Access (2020).

[14] Y. Fang, H. Zhang, J. Xie, M. Lin, L. Ying, P. Pang and W. Ji, "Sensitivity of chest CT for COVID-19: comparison to RT-PCR", Radiology (2020), 200432.

[15] Afshin Shoeibi, Marjane Khodatars, Roohallah Alizadehsani, Member, IEEE, Navid Ghassemi, Mahboobeh Jafari, Parisa Moridian, Ali Khadem, Delaram Sadeghi, Sadiq Hussain, Assef Zare, Zahra Alizadeh Sani, Javad Bazeli and Fahime Khozeimeh, Abbas Khosravi, Member, IEEE, Saeid Nahavandi, Fellow, IEEE, U. Rajendra Acharya, Senior Member, IEEE, Peng Shi, Fellow, IEEE, "Automated Detection and Forecasting of COVID-19 using Deep Learning Techniques", arXiv:2007.10785v3 (2020)

[16] Doremalen N van, Morris DH, Holbrook MG, Gamble A, Williamson BN., "Aerosol and surface stability of SARS-CoV-2 as compared with SARS-CoV-1", *N Engl J Med*. (2020) 382:1564–7. doi: 10.1056/NEJMc2004973

[17] Zhao CZ, Fang XC, Wang D, Tang F Di, Wang XD, "Involvement of type II pneumocytes in the pathogenesis of chronic

 DOI : 10.35291/2454-9150.2022.0025

ISSN : 2454-9150 Vol-07, Issue-10, JAN 2022

obstructive pulmonary disease", *Respir Med*. (2010) 104:1391–5. doi: 10.1016/j.rmed.2010.06.018

[18] Wölfel R, Corman VM, Guggemos W, Seilmaier M, Zange S, Müller MA, et al, "Virological assessment of hospitalized patients with COVID-2019", *Nature*. (2020) 581:465–9. doi: 10.1038/s41586-020-2196-x

[19] Xu Z, Shi L, Wang Y, Zhang J, Huang L, Zhang C, et al, "Pathological findings of COVID-19 associated with acute respiratory distress syndrome", *Lancet Respir Med*. (2020) 8:420–2. doi: 10.1016/S2213-2600(20)30076-X

[20] Shi S, Qin M, Shen B, Cai Y, Liu T, Yang F, et al, "Association of cardiac injury with mortality in hospitalized patients with COVID-19 in Wuhan, China", *JAMA Cardiol*. (2020) 25:e200950. doi: 10.1001/jamacardio.2020.0950

[21] Chen CY, Wang FL, Lin CC., "Chronic hydroxychloroquine use associated with QT prolongation and refractory ventricular arrhythmia", *Clin Toxicol*. (2006) 44:173–5. doi: 10.1080/15563650500514558

[22] Klok FA, Kruip MJHA, van der Meer NJM, Arbous MS, Gommers DAMPJ, Kant KM, et al, "Incidence of thrombotic complications in critically ill ICU patients with COVID-19", *Thromb Res*. (2020) 191:145–7. doi: 10.1016/j.thromres.2020.04.041

[23] Viner RM, Whittaker E, "Kawasaki-like disease: emerging complication during the COVID-19 pandemic", *Lancet*. (2020) 6736:19–20. doi: 10.1016/S0140-6736(20)31129-6

[24] Bökenkamp A, "Proteinuria—take a closer look!", *Pediatr Nephrol*. (2020) 35:533–41. doi: 10.1007/s00467-019-04454-w

[25] Sun J, Zhu A, Li H, Zheng K, Zhuang Z, Chen Z, et al., "Isolation of infectious SARS-CoV-2 from urine of a COVID-19 patient", *Emerg Microbes Infect*. (2020) 9:991–3. doi: 10.1080/22221751.2020.1760144

[26] Su H, Yang M, Wan C, Yi L-X, Tang F, Zhu H-Y, et al., "Renal histopathological analysis of 26 postmortem findings of patients with COVID-19 in China", *Kidney Int*. (2020) 21:1–9. doi: 10.1016/j.kint.2020.04.003

[27] Xu L, Liu J, Lu M, Yang D, Zheng X., "Liver injury during highly pathogenic human coronavirus infections", *Liver Int*. (2020) 40:998–1004. doi: 10.1111/liv.14435

[28] Abdel Galil SM, "Hydroxychloroquine-induced toxic hepatitis in a patient with systemic lupus erythematosus: a case report" *Lupus*. (2015) 24:638–40. doi: 10.1177/0961203314561667

[29] Lu CW, Liu XF, Jia ZF, "2019-nCoV transmission through the ocular surface must not be ignored", *Lancet*. (2020) 395:e39. doi: 10.1016/S0140-6736(20)30313-5

[30] Bacherini D, Biagini I, Lenzetti C, Virgili G, Rizzo S, Giansanti F., "The COVID-19 Pandemic from an ophthalmologist's perspective", *Trends Mol Med*. (2020) 26:529–31. doi: 10.1016/j.molmed.2020.03.008

[31] Lin L, Jiang X, Zhang Z, Huang S, Zhang Z, Fang Z, et al, "Gastrointestinal symptoms of 95 cases with SARS-CoV-2 infection", *Gut Immun*. (2020) 69:997–1001. doi: 10.1136/gutjnl-2020-321013

[32] Carvalho A, Alqusairi R, Adams A, Paul M, Kothari N, Peters S, et al, "SARS-CoV-2 gastrointestinal infection causing hemorrhagic colitis: implications for detection and transmission of COVID-19 disease", *Am J Gastroenterol*. (2020) 115:942–6. doi: 10.14309/ajg.0000000000000667

[33] Xiao F, Tang M, Zheng X, Liu Y, Li X, Shan, "Evidence for gastrointestinal infection of SARS-CoV-2", *Gastroenterology*. (2020) 158:1831–3.e3. doi: 10.1053/j.gastro.2020.02.055

[34] Landa N, Mendieta-eckert M, Fonda-pascual P, Aguirre T, "Chilblain-like lesions on feet and hands during the COVID-19 pandemic", *Int J Dermatol*. (2020) 59:739–43. doi: 10.1111/ijd.14937

[35] Bouaziz JD, Duong T, Jachiet M, Velter C, Lestang P, Cassius C, et al, "Vascular skin symptoms in COVID-19: a french observational study", *J Eur Acad Dermatol Venereol*. (2020) 34:e252–4. doi: 10.1111/jdv.16544

[36] Mao L, Jin H, Wang M, Hu Y, Chen S, He Q, et al, "Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan, China", *JAMA Neurol*. (2020) 77:1–9. doi: 10.1001/jamaneurol.2020.1127

[37] Costa KM, Accorsi-Mendonça D, Moraes DJA, Machado BH, "Evolution and physiology of neural oxygen sensing", *Front Physiol*. (2014) 5:302. doi: 10.3389/fphys.2014.00302

[38]Benghanem S, Mazeraud A, Azabou E, Chhor V, Shinotsuka CR, Claassen J, et al, "Hepatic dysfunction in critically ill patients", *Crit Care*. (2020) 24:5. doi: 10.1186/s13054-019-2718-9

[39] Siegel, D., Hui, H. C., Doerffler, E., Clarke, M. O., Chun, K., Zhang, L., et al, "Discovery and synthesis of a phosphoramidate prodrug of a pyrrolo[2,1-f][triazin-4-amino] adenine c-nucleoside (GS-5734) for the treatment of Ebola and emerging viruses", *J. Med. Chem.* (2017) 60, 1648–1661. doi:10.1021/acs.jmedchem.6b01594

[40] Sanders, J. M., Monogue, M. L., Jodlowski, T. Z., and Cutrell, J. B, "Pharmacologic Treatments for coronavirus disease 2019 (COVID-19): a review", *JAMA*. (2020) 323, 1824–1836. doi:10.1001/jama.2020.6019

[41] Wang, M., Cao, R., Zhang, L., Yang, X., Liu, J., Xu, M., et al, "Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) *in vitro", Cell Res.* (2020) 30, 269–271. doi:10.1038/s41422-020-0282-0

[42] Mentre, F., Taburet, A. M., Guedj, J., Anglaret, X., Keita, S., de Lamballerie, X., et al, "Dose regimen of favipiravir for Ebola virus disease", *Lancet Infect*. (2015). 15, 150–151. doi:10.1016/S1473-3099(14)71047-3

[43] Li, G., and De Clercq, E, "Therapeutic options for the 2019 novel coronavirus (2019-nCoV)", *Nat. Rev. Drug Discov*. 19, (2020) 149–150. doi:10.1038/d41573-020-00016-0

[44] Hu, T. Y., Frieman, M., and Wolfram, J, "Insights from nanomedicine into chloroquine efficacy against COVID-19", *Nat. Nanotechnol.* 15, (2020). 247–249. doi:10.1038/s41565-020-0674-9

[45] Gautret, P., Lagier, J. C., Parola, P., Hoang, V. T., Meddeb, L., Mailhe, M., et al, "Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial", *Int. J. Antimicrob. Agents* 20, (2020). 105949. doi:10.1016/j.ijantimicag.2020.105949

 DOI : 10.35291/2454-9150.2022.0025