Hormozgan Medical Journal

doi 10.34172/hmj.2022.19

Hormozgan Med J. 2022; 26(2): 113-118

Review Article

COVID-19 and Hepatic Encephalopathy: A Narrative Review

Nahid Davoodian[1,2], **Elias Kargar-Abargouei**[3,4], **Maryam Arab Firouzjaei**[3,5*]

[1]Endocrinology and Metabolism Research Center, Hormozgan University of Medical Sciences, Bandar Abbas, Iran
[2]Department of Clinical Biochemistry, Faculty of Medicine, Hormozgan University of Medical Sciences, Bandar Abbas, Iran
[3]Molecular Medicine Research Center, Hormozgan Health Institute, Hormozgan University of Medical Sciences, Bandar Abbas, Iran
[4]Department of Anatomical Sciences, Faculty of Medicine, Hormozgan University of Medical Sciences, Bandar Abbas, Iran
[5]Department of Physiology, Faculty of Medicine, Hormozgan University of Medical Sciences, Bandar Abbas, Iran

Abstract

The 2019 novel coronavirus (COVID-19) has been known as a highly pandemic virus that is characterized by a severe multiorgan pathology. Generally, cardio-respiratory complications are the dominant manifestations in patients infected with COVID-19. Since the coronavirus targets angiotensin-converting enzyme (ACE) receptors, however, the virus is also likely to exhibit multiorgan complications. Some retrospective cohorts as well as case studies have shown varying degrees of increased alanine transaminase (ALT)/aspartate transaminase (AST) in COVID-19 infections. A limited number of histopathological studies examining the liver have also reported an acute portal necrosis of this organ. Some other studies investigating the patients with COVID-19 have documented an acute hepatic encephalopathy with altered mental status. Beyond doubt, having a greater awareness of these complications positively contributes to timely and effective management and treatment of the patients. The present review article, therefore, aimed to highlight the consequences of developing hepatic encephalopathy for patients with COVID-19, its possible multifaceted mechanisms, and the management of neurological complications in these infected patients.

Keywords: COVID-19, Hepatic encephalopathy, Neurological complication

***Correspondence to**
Maryam Arab Firouzjaei,
Tel: +989118986338,
Fax: +98763366 8478,
Email: mfiruzjaee@gmail.com,
mfirouzjaei@hums.ac.ir

Received February 17, 2021, **Accepted**: April 20, 2021, **Published Online**: June 29, 2022

Background

COVID-19, a severe acute respiratory syndrome (SARS) caused by SARS-CoV-2, was first reported in China. It is now regarded as a global pandemic responsible for infecting more than 105 million people worldwide as well as resulting in the confirmed death of almost 2 312 278 ones as of 8 February 2021 (1). Studies have shown that 70% of the infected patients suffering from COVID-19 present with mild to moderate respiratory signs, while the rest develop severe to fatal respiratory and systemic diseases depending on their personal genetic makeup, stage of infection, and inadequate management. In general, coronaviruses (CoVs) are considered as members of the Coronaviridae family with non-segmented, single-stranded, positive-sense, and enveloped RNA, that can infect humans and animals (1). The majority of human CoVs, including hCoV-229E, hCoV-OC43, hCoV-NL63, and hCoV-HKU1, causes mild respiratory syndrome; however, some studies have shown that three other cases, such as SARS-CoV, MERS-CoV, and COVID-19 may result in acute respiratory distress with a high lethal potential (2, 3). It is noteworthy that COVID-19, similar to SARS-CoV, binds through its s-proteins to the angiotensin-converting enzyme 2 (ACE2) on the human cells membrane (4). ACE2 receptor widely present in the vascular endothelial cells of many organs, including the skin, spleen, liver, kidney, lymph nodes, thymus, bone marrow, brain, and – especially – in the epithelium of the lung, jejunum and duodenum (5). In effect, the wide presence of ACE2 suggests that COVID-19 can spread throughout the human body through the bloodstream. This suggestion has been confirmed by several recent studies on neurological manifestations in these patients, despite the fact that respiratory failure is the most expected manifestation in patients with COVID-19 (6-9). These neurological symptoms are the systemic complications of COVID-19, and are considered to be the end result of direct invasion of the virus to the central nervous system (CNS) or associated with the immune-mediated ill (10). Some studies have documented the occurrence of hepatic encephalopathy among the patients infected with COVID-19 (11, 12). Hepatic encephalopathy is a pathological process in the brain that is associated with liver dysfunction. It often occurs within hours or days and may cause changes in personality, behavior, cognition, or consciousness. Plasma ammonia levels are considered as important factors negatively contributing to the pathogenesis of hepatic encephalopathy, and ammonia

concentrations are high in the systemic circulation of the patients with hepatic encephalopathy (< 76 µmol/L) (13).

Objectives

The present revie aimed to discuss the COVID-19-induced hepatic encephalopathy as well as the possible mechanisms by which COVID-19 was able to induce hepatic encephalopathy.

The Neurological Complications of COVID-19 Infection

Given the high homology in the sequence between COVID-19 and SARS-CoV, it can be expected that similar clinical manifestations for COVID-19 and SARS-COV infections (14). Most patients infected with COVID-19 develop common symptoms at the onset of the disease, including fever, dry cough, and fatigue. According to the results from clinical studies in China, diarrhea occurs in a limited number of the patients (approximately 3%) (3,15). In general, COVID-19 is accompanied with pneumonia and abnormal computed tomography (CT) of the chest. Some studies have reported the development of neurological complications in patients, including headache, loss of taste and smell, weakness, and no common respiratory manifestation (8). The results from a retrospective study conducted in Wuhan, China showed that out of 214 cases infected with COVID-19, 36.4% of the cases had neurological symptoms classified as CNS, peripheral nervous system (PNS), and musculoskeletal complications. The most common symptoms in patients with CNS involvement were vertigo and headache. Likewise, hypogeusia and hyposmia were observed to be common symptoms in patients with PNS signs. (8). These results were indicative of CNS involvement in patients with COVID-19 infection, which may have led to neurological disease.

The Mechanisms of Hepatic Encephalopathy

COVID-19 virus may directly or indirectly affect the nervous system through various pathways, and many studies have demonstrated that the virus is capable of reaching the CNS through blood circulation, nerve fibers, or direct invasion via the olfactory bulb (16). It is noteworthy that an indirect invasion to the CNS may be carried out through hypoxemia, immune-mediated injury, or multi-organ involvement with a potential for CNS complications (10, 17). It is noteworthy that in the COVID-19 infection, the liver is the second organ affected after the lungs, which can lead to hepatic encephalopathy (18).

Angiotensin Converting Enzyme 2 Receptor Role to Entrance COVID-19 Into Liver

The mechanism that indicates organ-specific affinity for COVID-19 is associated with ACE2 receptors. There is evidence for the presence of ACE2 receptors in the brain – in nerve and glial cells, in particular – as well as in the liver; in fact, a strong relationship has been identified between COVID-19 and these receptors causing the infection (16, 18).

Liver damage is one of the complications that may occur in the patients infected with coronavirus. This complication might be caused by a direct damage to liver cells due to the spread of infectious virus. Previous studies have demonstrated that about 2 to 10 percent of the patients with COVID-19 are also afflicted with diarrhea, and SARS-CoV-2 RNA can be found in their blood and stool samples (19). This finding suggests that the virus is likely present in the liver cells. SARS-CoV-2 and SARS-CoV enter the target cells via binding to the ACE2 receptor (20), where the virus multiplies and eventually infects the upper respiratory system as well as the lung tissue. Subsequently, clinical signs and symptoms begin in the patient. The pathological evidence from infected patients is indicative of the presence of the virus in liver tissue; however, the virus titer in liver tissue has been reported to be relatively low (21). It should be noted that the virus particles in liver tissue have not been measurable in patients infected with MERS (22). Studies examining 56 patients infected with COVID-19 during hospitalization period showed that only one patient (1.8%) had increased alkaline phosphatase levels (23). However, pathological finding from the liver tissue of a patient who had died of COVID-19 confirmed the absence of viral compounds in the liver (24).

Immune-Mediated Encephalopathy Followed Liver Damage in Infected Patient With COVID-19

Immune-mediated inflammation, like cytokine storms and hypoxia associated with respiratory failure, may also contribute to the development of liver damage or even lead to liver failure in patients with severe COVID-19 (23). Severe viral infections cause systemic inflammatory response syndrome (SIRS). Studies have confirmed that severe pneumonia could result in SIRS via CoVs infection (25). In this regard, previous findings have suggested the early use of anti-inflammatory drugs as a method to prevent immune injury as well as decrease the risk of CNS damage in patients with COVID-19 (26). In addition, many studies have reported a high mortality rate due to viral infections caused by both SARS-CoV and COVID-19 viruses, since these diseases multiple organ failure following SIRS caused by the virus or SIRS-like immune disorders (27, 28). This point is well-supported by the fact that the level of interleukin (IL)-6 as an important factor of the cytokine storm family is directly associated with the severity of COVID-19 disease (29). According to another study, hypercytokinemia was detected in COVID-19 patients (30).

An important feature of the CoVs virus is its potency to infect macrophages, astrocytes, and microglia in the CNS. Studies have shown that these viruses are able to

activate glial cells and, thus, lead to the production of proinflammatory cytokines from these cells (31). Another in vitro study on glial cells following CoVs infection found a significant increase in inflammatory agents like IL-6, IL-15, IL-12, and TNF-α in these cells. (32). Given the high homology between COVID-19 and SARS-CoV, it is important to consider the neurological manifestations previously confirmed for other COVs, particularly in elderly cases who are afflicted with COVID-19 and are prone to neurological manifestations.

Liver Injury of COVID-19 That Can Cause Hepatic Encephalopathy

In severe cases of COVID-19, respiratory distress or hypoxia occurs nearly seven days after the onset of the disease, and these complications eventually lead to acute respiratory distress syndrome, metabolic acidosis, septic shock, and even death (3). Recent studies have shown that the rate of liver damage varies from 14.8 to 53 percent, which is mainly due to elevated alanine transaminase (ALT)/ aspartate transaminase (AST) levels as well as bilirubin levels (3, 15, 20, 33-35). Serum albumin levels are also reduced in patients with high disease severity (26.3-30.9 g/L) (36). Some study results have indicated that the possibility of liver damage in severe cases of COVID-19 is significantly higher than that in mild cases (3, 33). As for the fatal cases of COVID-19, several studies have reported that 58.06% (37) and 78% (38) of the patients sustain liver damage. A recent research has also shown that serum ALT and AST levels in a severe COVID-19 patient increases to 7590 U/L and 1445 U/L, respectively (36). To date, few studies have examined the mechanism of COVID-19-related liver damage. It has been confirmed that SARS-CoV-2, similar to SARS-CoV, uses ACE2 as a receptor to enter liver tissue (37). A previous study has also confirmed that liver cells and bile duct cells express ACE2 (39). However, the expression of the ACE2 receptor in bile duct cells is much higher than that in hepatocytes, although it is lower in type 2 alveolar cells in the lung. Bile duct epithelial cells have been determined to be the most important cells in regenerating the liver tissue and inducing the immune reactions (40). These findings suggest that the liver damage in COVID-19 patients may be secondary to the bile duct cell damage. In severe COVID-19 disease, on the other hand, an inflammatory cytokine storm occurs (41); however, further studies are needed to address this factor in liver damage. The results from postmortem biopsy in COVID-19 patients, microvascular steatosis, as well as mild lobular and portal activity have demonstrated that these manifestation could be due to SARS-CoV-2 infection or liver damage caused by drug toxicity (42). It is now a common knowledge that COVID-19 is treated with a wide range of antibiotics, antivirals, and steroids. All these drugs may have potential to exert positive effects on liver damage; however, the efficacy of the given drugs has not yet been medically confirmed (43). In effect, a recent report has suggested that liver damage in COVID-19 cases may be caused by lopinavir/ritonavir which is used as an antiviral to treat SARS-CoV-2 infection (34).

The Evidences of Hepatic Encephalopathy in Patient With COVID-19 Infection

Hepatic encephalopathy is known as a serious neuropsychiatric syndrome, which can occur as the result of an acute inflammation (13). Studies have revealed that the disease occurs in cases of acute liver failure following a viral infection. Some other studies have also demonstrated that hepatic encephalopathy may afflict the patients infected with SARS-CoV-2 (11, 44). The first case of hepatic encephalopathy was identified in a patient with COVID-19 at Ditan Hospital in Beijing, by genomic sequencing of the virus in a cerebrospinal fluid sample (45). A 55-year-old woman with COVID-19 was reported to have been diagnosed with hepatic encephalopathy based on her clinical history, laboratory tests, and radiology. The patient also showed neurological symptoms including anxiety, delirium, confusion, and seizures. Significant increases were also detected in elevated levels of aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, and plasma ammonia, as well as in inflammatory factors such as ILs 6 and 10 (46). Another case proving the association of COVID-19 with hepatic encephalopathy was a 32-years-old African American male patient diagnosed with COVID-19 by analyzing the reverse transcription polymerase chain reaction (RT-PCR) as well as the qualitative IgM, computerized tomography (CT) of his chest and clinical symptom. In this patient, moreover, increases were observed in the levels of C-reactive protein, IL 6, ferritin, and D-dimer. Reports from the fourth day of his illness state showed progress in behavioral and cognitive dysfunction, and the Glasgow Coma Scale was found to be 13/15. The brain CT confirmed the cerebral edema as well as the symmetric hypoattenuation within the medial thalami signs of intracerebral hemorrhage (11).

An Iranian boy aged 14-year-old was significantly reported to present with an abdominal protrusion, lower extremities pitting edema, icter, and weight gain. He had no history of fever, nausea, vomiting, oliguria, myalgia, and dyspnea, although he was in contact with his family members with cough. His chest radiography revealed diffuse haziness through the left lung field. Bilateral, multifocal, and subpleural ground-glass opacity with mild pleural effusion was detected during his spiral chest CT scan without contrast, which was strongly suggestive of COVID-19. His nasopharyngeal swab sample RT-PCR confirmed the diagnosis of COVID-19 pneumonia, and the serial nasopharyngeal sample test for COVID-19 was found positive for three consecutive weeks. The results of several abdominal paracenteses were transudative and clear. There was every indication that the patient needed

an emergency liver transplantation, and his condition subsequently worsened despite an initial improvement. He gradually developed encephalopathy with mood and mental status changes such as day time sleeping, lethargy, tremor, and respiratory distress. Unfortunately, the patient died after 18 days of hospitalization with features of refractory pulmonary hemorrhage (44).

Evaluation and Management of Hepatic Encephalopathy in Patients Infected With COVID-19

Since COVID-19 is a very contagious and serious virus with a critical incubation period, it is necessary to take preventive measures, establish early diagnosis, and provide timely treatment in order for properly dealing with it. To date, the most standard diagnostic method for confirming COVID-19 infection has been nucleic acid amplification tests. Due to the high probability of error occurrence in this method, however, the negative results of this test cannot rule out the probability of infection and, therefore, repeated tests may be required (47). An important point to consider is that the manifestations of this disease in COVID-19-infected patients vary greatly from person to person. Similarly, most studies have identified respiratory symptoms as the primary complications in patients. Although, there is ample finding that a limited number of patients have other manifestations, including the neurological complications that were fully described above, which can occur following acute liver failure (6, 8) . Importantly, neurological involvement is more common in patients with severe degree of infections, which may cause cerebral hemorrhage, ischemic stroke, and even death (8, 48, 49). In addition, a significant increase in inflammatory factors is an important cause of clinical exacerbation of the disease (50). It is noteworthy that neurological disorders may be nonspecific in the early stages of COVID-19 infection, which can lead to misdiagnosis and delayed treatment. Therefore, careful physical examination, medical history review, as well as imaging take on added importance at the time of diagnosing liver failure and subsequent hepatic encephalopathy in order for properly managing and timely treating the patients (51).

Conclusion

Overall, the available evidence suggested that the CNS was sensitive to COVID-19. According to our findings, most cases infected with COVID-19 may have shown minor and nonspecific neurological complications at the onset of the disease, leading to misdiagnosis and delayed treatment. Although neurological involvement had been previously reported more frequently in patients with severe infections, it was determined that neurological manifestations were also likely to occur among these patients due to liver failure. Given the scant evidence existed for neurologic presentation due to liver injury in patients infected with COVID-19, it was recommended that further studies be conducted to elucidate the neurobiology and mechanisms of hepatic encephalopathy, prevent its occurrence, as well as manage and treat it timely.

Acknowledgement

The authors gratefully appreciate all the doctors, nurses, and health staff of Hormozgan University of Medical Sciences for their efforts and dedication to treat patients with COVID-19.

Conflict of Interests

The authors declare that they have no conflict of interests.

Ethical Approval

Not applicable.

Funding/Support

None.

References

1. Yang D, Leibowitz JL. The structure and functions of coronavirus genomic 3′ and 5′ ends. Virus Res. 2015;206:120-33. doi: 10.1016/j.virusres.2015.02.025.
2. Corman VM, Lienau J, Witzenrath M. [Coronaviruses as the cause of respiratory infections]. Internist (Berl). 2019;60(11):1136-45. doi: 10.1007/s00108-019-00671-5.
3. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020;395(10223):497-506. doi: 10.1016/s0140-6736(20)30183-5.
4. Magrone T, Magrone M, Jirillo E. Focus on receptors for coronaviruses with special reference to angiotensin-converting enzyme 2 as a potential drug target-a perspective. Endocr Metab Immune Disord Drug Targets. 2020;20(6):807-11. doi: 10.2174/1871530320666200427112902.
5. Hamming I, Timens W, Bulthuis ML, Lely AT, Navis G, van Goor H. Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis. J Pathol. 2004;203(2):631-7. doi: 10.1002/path.1570.
6. Chen T, Wu D, Chen H, Yan W, Yang D, Chen G, et al. Clinical characteristics of 113 deceased patients with coronavirus disease 2019: retrospective study. BMJ. 2020;368:m1091. doi: 10.1136/bmj.m1091.
7. Conde Cardona G, Quintana Pájaro LD, Quintero Marzola ID, Ramos Villegas Y, Moscote Salazar LR. Neurotropism of SARS-CoV 2: mechanisms and manifestations. J Neurol Sci. 2020;412:116824. doi: 10.1016/j.jns.2020.116824.
8. Mao L, Wang M, Chen S, He Q, Chang J, Hong C, et al. Neurological manifestations of hospitalized patients with COVID-19 in Wuhan, China: a retrospective case series study. medRxiv [Preprint]. February 25, 2020. Available from: https://www.medrxiv.org/content/10.1101/2020.02.22.20026500v1.
9. Wang W, Xu Y, Gao R, Lu R, Han K, Wu G, et al. Detection of SARS-CoV-2 in different types of clinical specimens. JAMA. 2020;323(18):1843-4. doi: 10.1001/jama.2020.3786.
10. Ellul MA, Benjamin L, Singh B, Lant S, Michael BD, Easton A, et al. Neurological associations of COVID-19. Lancet Neurol. 2020;19(9):767-83. doi: 10.1016/s1474-4422(20)30221-0.
11. Gamboa E, Montelongo D, Berjaoui H, Varon DS, Gathe JC Jr, Varon J. COVID-19-induced hepatic encephalopathy: a case report. Crit Care Shock. 2020;23(3):154-7.
12. Al Mazrouei SS, Saeed GA, Al Helali AA, Ahmed M. COVID-19-associated encephalopathy: neurological manifestation

of COVID-19. Radiol Case Rep. 2020;15(9):1646-9. doi: 10.1016/j.radcr.2020.07.009.
13. Cordoba J. Hepatic encephalopathy: from the pathogenesis to the new treatments. ISRN Hepatol. 2014;2014:236268. doi: 10.1155/2014/236268.
14. Mousavizadeh L, Ghasemi S. Genotype and phenotype of COVID-19: their roles in pathogenesis. J Microbiol Immunol Infect. 2021;54(2):159-63. doi: 10.1016/j.jmii.2020.03.022.
15. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, et al. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med. 2020;382(18):1708-20. doi: 10.1056/NEJMoa2002032.
16. Wu Y, Xu X, Chen Z, Duan J, Hashimoto K, Yang L, et al. Nervous system involvement after infection with COVID-19 and other coronaviruses. Brain Behav Immun. 2020;87:18-22. doi: 10.1016/j.bbi.2020.03.031.
17. Davoodian N, Arab Firouzjaei M, Negahi A. Neurological involvement of patients with COVID-19: proposed neuroinvasive mechanisms and management. Hormozgan Med J. 2020;24(4):107977-. doi: 10.5812/hmj.107977.
18. Li J, Fan JG. Characteristics and mechanism of liver injury in 2019 coronavirus disease. J Clin Transl Hepatol. 2020;8(1):13-7. doi: 10.14218/jcth.2020.00019.
19. Yeo C, Kaushal S, Yeo D. Enteric involvement of coronaviruses: is faecal-oral transmission of SARS-CoV-2 possible? Lancet Gastroenterol Hepatol. 2020;5(4):335-7. doi: 10.1016/s2468-1253(20)30048-0.
20. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. JAMA. 2020;323(11):1061-9. doi: 10.1001/jama.2020.1585.
21. Chau TN, Lee KC, Yao H, Tsang TY, Chow TC, Yeung YC, et al. SARS-associated viral hepatitis caused by a novel coronavirus: report of three cases. Hepatology. 2004;39(2):302-10. doi: 10.1002/hep.20111.
22. Alsaad KO, Hajeer AH, Al Balwi M, Al Moaiqel M, Al Oudah N, Al Ajlan A, et al. Histopathology of Middle East respiratory syndrome coronovirus (MERS-CoV) infection-clinicopathological and ultrastructural study. Histopathology. 2018;72(3):516-24. doi: 10.1111/his.13379.
23. Zhang C, Shi L, Wang FS. Liver injury in COVID-19: management and challenges. Lancet Gastroenterol Hepatol. 2020;5(5):428-30. doi: 10.1016/s2468-1253(20)30057-1.
24. Tabari M, Khanmohammadi Sh, Araghi F, Dadkhahfar S, Tvangar SM. Pathological features of COVID-19: A concise review. Patholgy- Research and Practice. 2020;216:512-21. doi: 10.1016/j.prp.2020.153097.
25. Fu Y, Cheng Y, Wu Y. Understanding SARS-CoV-2-mediated inflammatory responses: from mechanisms to potential therapeutic tools. Virol Sin. 2020;35(3):266-71. doi: 10.1007/s12250-020-00207-4.
26. Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ. COVID-19: consider cytokine storm syndromes and immunosuppression. Lancet. 2020;395(10229):1033-4. doi: 10.1016/s0140-6736(20)30628-0.
27. 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(6):683-90. doi: 10.1001/jamaneurol.2020.1127.
28. Yin CH, Wang C, Tang Z, Wen Y, Zhang SW, Wang BE. [Clinical analysis of multiple organ dysfunction syndrome in patients suffering from SARS]. Zhongguo Wei Zhong Bing Ji Jiu Yi Xue. 2004;16(11):646-50.
29. Tang W, Hu T, Hu B, Jin C, Wang G, Xie C, et al. Prevalence and correlates of PTSD and depressive symptoms one month after the outbreak of the COVID-19 epidemic in a sample of home-quarantined Chinese university students. J Affect Disord. 2020;274:1-7. doi: 10.1016/j.jad.2020.05.009.
30. Yang Y, Shen C, Li J, Yuan J, Yang M, Wang F, et al. Exuberant elevation of IP-10, MCP-3 and IL-1ra during SARS-CoV-2 infection is associated with disease severity and fatal outcome. medRxiv [Preprint]. March 6, 2020. Available from: https://www.medrxiv.org/content/10.1101/2020.03.02.20029975v1.
31. Li Y, Fu L, Gonzales DM, Lavi E. Coronavirus neurovirulence correlates with the ability of the virus to induce proinflammatory cytokine signals from astrocytes and microglia. J Virol. 2004;78(7):3398-406. doi: 10.1128/jvi.78.7.3398-3406.2004.
32. Bohmwald K, Gálvez NMS, Ríos M, Kalergis AM. Neurologic alterations due to respiratory virus infections. Front Cell Neurosci. 2018;12:386. doi: 10.3389/fncel.2018.00386.
33. Cai Q, Huang D, Ou P, Yu H, Zhu Z, Xia Z, et al. COVID-19 in a designated infectious diseases hospital outside Hubei province, China. Allergy. 2020;75(7):1742-52. doi: 10.1111/all.14309.
34. Fan Z, Chen L, Li J, Tian C, Zhang Y, Huang S, et al. Clinical features of COVID-19-related liver damage. medRxiv [Preprint]. February 28, 2020. Available from: https://www.medrxiv.org/content/10.1101/2020.02.26.20026971v2.
35. Cao W, Shi L, Chen L, Xu X, Wu Z. Clinical features and laboratory inspection of novel coronavirus pneumonia (COVID-19) in Xiangyang, Hubei. medRxiv [Preprint]. February 25, 2020. Available from: https://www.medrxiv.org/content/10.1101/2020.02.23.20026963v1.
36. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet. 2020;395(10223):507-13. doi: 10.1016/s0140-6736(20)30211-7.
37. Huang Y, Yang R, Xu Y, Gong P. Clinical characteristics of 36 non-survivors with COVID-19 in Wuhan, China. medRxiv [Preprint]. March 5, 2020. Available from: https://www.medrxiv.org/content/10.1101/2020.02.27.20029009v2.
38. Zhang B, Zhou X, Qiu Y, Feng F, Feng J, Jia Y, et al. Clinical characteristics of 82 death cases with COVID-19. medRxiv [Preprint]. February 27, 2020. Available from: https://www.medrxiv.org/content/10.1101/2020.02.26.20028191v1.
39. Chai X, Hu L, Zhang Y, Han W, Lu Z, Ke A, et al. Specific ACE2 expression in cholangiocytes may cause liver damage after 2019-nCoV infection. bioRxiv [Preprint]. February 4, 2020. Available from: https://www.biorxiv.org/content/10.1101/2020.02.03.931766v1.
40. Banales JM, Huebert RC, Karlsen T, Strazzabosco M, LaRusso NF, Gores GJ. Cholangiocyte pathobiology. Nat Rev Gastroenterol Hepatol. 2019;16(5):269-81. doi: 10.1038/s41575-019-0125-y.
41. Liu J, Li S, Liu J, Liang B, Wang X, Wang H, et al. Longitudinal characteristics of lymphocyte responses and cytokine profiles in the peripheral blood of SARS-CoV-2 infected patients. EBioMedicine. 2020;55:102763. doi: 10.1016/j.ebiom.2020.102763.
42. 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(4):420-2. doi: 10.1016/s2213-2600(20)30076-x.
43. Yang X, Yu Y, Xu J, Shu H, Xia J, Liu H, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2

pneumonia in Wuhan, China: a single-centered, retrospective, observational study. Lancet Respir Med. 2020;8(5):475-81. doi: 10.1016/s2213-2600(20)30079-5.
44. Dara N, Sharifi N, Ghanbari Boroujeni M, Hosseini A, Sayyari A. COVID-19 pneumonia in a child with hepatic encephalopathy: a case study. Iran J Child Neurol. 2021;15(1):113-8. doi: 10.22037/ijcn.v15i1.30879.
45. Wu Y, Xu X, Chen Z, Duan J, Hashimoto K, Yang L, et al. Nervous system involvement after infection with COVID-19 and other coronaviruses. Brain Behav Immun. 2020;87:18-22. doi: 10.1016/j.bbi.2020.03.031.
46. del Carmen Dominguez-Horta M. CIGB-258, An Immunomodulatory Peptide for the Treatment of a COVID-19-associated Hepatic Encephalopathy: A Case Report. Preprints. 2020;2020090240. Available from: https://www.preprints.org/manuscript/202009.0240/v1.
47. World Health Organization (WHO). Laboratory Testing for Coronavirus Disease 2019 (COVID-19) in Suspected Human Cases: Interim Guidance, 2 March 2020. WHO; 2020.
48. TunÇ A, ÜnlÜbaŞ Y, Alemdar M, AkyÜz E. Coexistence of COVID-19 and acute ischemic stroke report of four cases. J Clin Neurosci. 2020;77:227-9. doi: 10.1016/j.jocn.2020.05.018.
49. Sharifi-Razavi A, Karimi N, Rouhani N. COVID-19 and intracerebral haemorrhage: causative or coincidental? New Microbes New Infect. 2020;35:100669. doi: 10.1016/j.nmni.2020.100669.
50. Jin H, Hong C, Chen S, Zhou Y, Wang Y, Mao L, et al. Consensus for prevention and management of coronavirus disease 2019 (COVID-19) for neurologists. Stroke Vasc Neurol. 2020;5(2):146-51. doi: 10.1136/svn-2020-000382.
51. Khalili N, Haseli S, Bahrami-Motlagh H, Keshavarz E, Khalili N, Langroudi TF, et al. Neurologic involvement in COVID-19: radiologists' perspective. Acad Radiol. 2020;27(7):1051-3. doi: 10.1016/j.acra.2020.04.035.