Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.
Care for Patients with Stroke During the COVID-19 Pandemic: Physical Therapy and Rehabilitation Suggestions for Preventing Secondary Stroke

Chien-Chih Wang,*† Jian-Kang Chao,‡§ Mong-Lien Wang,†¶ Yi-Ping Yang,†¶ Chien-Shiu Chien,†¶ Wei-Yi Lai,†¶ Yi-Chiang Yang,# Yu-Hui Chang,|| Chen-Liang Chou,#** and Chung-Lan Kao,†#**††

Infection with the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causes the development of the novel 2019 coronavirus disease (COVID-19) and associated clinical symptoms, which typically presents as an upper respiratory syndrome such as pneumonia. Growing evidence indicates an increased prevalence of neurological involvement (e.g., in the form of stroke) during virus infection. COVID-19 has been suggested to be more than a lung infection because it affects the vasculature of the lungs and other organs and increases the risk of thrombosis. Patients with stroke are vulnerable to secondary events as a result not only of their poor vascular condition but also of their lack of access to rehabilitation resources. Herein, we review current knowledge regarding the pathophysiology of COVID-19, its possible association with neurological involvement, and current drug therapies. Suggestions are also offered regarding the potential for current neuromuscular therapies to be taught and practiced at home.

Key Words: COVID-19—Patients with stroke—Coagulopathy—Physical therapy—Rehabilitation
© 2020 Elsevier Inc. All rights reserved.

Introduction
The outbreak of the novel coronavirus disease (COVID-19) in 2019 has had a tremendous impact on public health.

The number of infected patients is continually increasing, and the total number of deaths has exceeded 250000 people as of March 2020. Reports on clinical symptoms have provided increasing evidence of neurological deficits, including cardiovascular events and the formation of peripheral nerve lesions.¹ Recent observations have also revealed a growing number of thrombotic events resulting in stroke among young adults, some of whom have been asymptomatic or have only had mild symptoms of COVID-19.² Although no recent data have definitively indicated whether the rate of infection with COVID-19 has been higher among patients with stroke, comorbidities such as hypertension, diabetes, and cardiovascular disease have been reported to be closely related to increased infection rates among patients with stroke.³,⁴ Secondary stroke risk may be increased not only because of the thrombotic properties of COVID-19 but also because of physical inactivity resulting from isolation or restricted access to hospital facilities and therapy among these patients.

This review discusses the relationship of COVID-19 to the neurological aspects of pathophysiology and immune
responses. To address the current concerns regarding a lack of access to drug therapy, some neurorehabilitation techniques can potentially be taught and practiced at home.

Pathophysiology and immune response

Coronaviruses are enveloped positive strand RNA viruses with the largest known RNA genome. The RNA genome of coronaviruses is highly variable and subject to recombination, which is a typical feature of RNA viruses. This feature enables them to quickly spread among humans and animals, sometimes leading to life-threatening conditions. However, some highly contagious and pathogenic strains are occasionally produced from recombination within intermediate hosts. The corona-like appearance with club-shaped spikes is the main feature of the virus. The nucleocapsids are helically symmetrical and are packed by the envelope of the virion. Among the functions of the structural proteins, the envelope has a crucial role in virus pathogenicity through the promotion of viral assembly and release.

The pathogenic lesions of coronavirus infection arise mainly from immunopathological events that result in fatal pneumonia. Pathogen-associated molecular patterns comprising viral RNA form during viral replication and trigger immune recognition. This results in the expression of type I interferon and proinflammatory cytokines for protection against infection by the virus, which constitutes the early stage of defense against the virus.

In some severe cases, the cytokine storm induced by interleukin 6 (IL-6) causes massive tissue damage, characterized by fever and multiple organ dysfunction. In addition, higher plasma levels of interleukin 2, interleukin 7, interleukin 10, GSCF, IP10, MCP1, MIP1A, and TNFα are observed in patients requiring admission to the intensive care unit.

Recent observations suggest that microvascular thrombolic processes may play a prominent role in respiratory failure induced by COVID-19. Venous thrombosis is indicated by the strong association among disease progression embolus, D-dimer levels, and chest computed tomography features. This infection-associated coagulopathy suggests that COVID-19 may be a thromboinflammatory process that initially affects lung perfusion and subsequently affects all organs of the body.

Role of Renin Angiotensin System and Angiotensin-Converting Enzyme 2 in the Neurological Effects of Covid-19

The renin-angiotensin system (RAS) in brain and peripheral organ played a fundamental role in regulating the electrolyte homeostasis and cardiovascular control. The classic axis with ACE(angiotensin), Angiotensin II (Ang II) and angiotensin type-1 receptor (ATIR) had the vasoconstrictor effect and overactivation this axis severs as an important role in acute ischemic stroke. In contrary, activation of the alternative axis included ACE2, Ang(1–7) and MAS receptor (MAS) results in vasodilation, anti-inflammation and angiogenesis response that may have protective effects against stroke.

ACE2 serves as the main receptor for the entry of the severe acute respiratory syndrome (SARS) coronavirus 2 (SARS-CoV-2) virus into human cells although COVID-19 was proposed associated with multiple receptors such as CD147 and salic acid. The ACE2–angiotensin pathway plays a neuroprotective role in patients with stroke. ACE2 is widely expressed in the cells of the central nervous system (CNS), and its expression has been shown to increase following stroke. Another study using samples from human patients with stroke revealed that ACE2 was markedly higher in patients with certain types of stroke, implying that ACE2 can be used as a diagnostic marker. Accordingly, ACE2 may serve as a link between SARS-CoV-2 infection and neurological effects in patients with stroke. A recent review examined whether an ACE inhibitor could reduce virus infection susceptibility by inhibiting this viral entry pathway. One multinational study of 8910 inpatients infected with COVID-19 worldwide was conducted and could not confirm the harmful association of ACE inhibitors or angiotensin-receptor blockers with COVID-19 mortality.

Possible Mechanism Underlying the Involvement of COVID-19 in the Development of Vascular Problems

Although the neurological effects in patients who have had a stroke directly induced by COVID-19 have not been reported, several indications have been made in recent studies. A case series study conducted early in a Wuhan hospital indicated that patients with more severe diseases developed neurological manifestations, including acute cerebrovascular accident (5.7%) and impaired consciousness (14.8%). The proposed mechanism was anterograde and retrograde virus infection of the CNS system through the hematogenous or retrograde route. Patients with COVID-19 and CNS involvement were observed to have lower lymphocyte and elevated D-dimer levels, indicating possible links with infection and neurological involvement.

The coagulopathy of COVID-19 was initially reported through observation of the increased incidence of pulmonary embolism in highly symptomatic ill patients. A link between thromboembolic events and influenza-associated pneumonia has been identified. Increased procoagulant profile such as D-dimer level and fibrin degradation products was observed in patients with COVID-ARDS, and this coagulopathy can be reversed after thromboprophylaxis prescription. Moreover, disseminated intravascular coagulopathy (DIC) characterized by severe thrombocytopenia and low platelet count due to the consumption of coagulation factors was also found in severe COVID-19 patients.
CARE FOR PATIENTS WITH STROKE DURING THE COVID-19 PANDEMIC

Vasculitis caused by the inflammation is considered to be an important mechanism in neurological manifestations. Previous reports on patients with SARS indicated widespread vascularity in many organs, which may directly affect blood supply to the brain. Moreover, the presence of hypertension or hypotension was also considered to be a crucial factor related to the occurrence of cerebrovascular events. A study conducted in Singapore revealed that 5 of 206 patients with SARS had large vessel lesions, and 3 of them had severe episodes of hypotension. Elevated blood pressure was also noted among a high proportion of critically ill patients and nonsurvivors. Moreover, cardiac abnormality and arrhythmia contribute to increased stroke incidence, which may be caused by critical illnesses such as hypoxia, metabolic derangement, and systemic inflammation.

An increasing number of cases of sudden loss of olfactory function have been reported. A possible mechanism was proposed to be related to central cortical neurons and the expression of olfactory receptors possessing ACE2 receptors. Although damage to primary epithelial cells was considered, MRI revealed no olfactory bulb or tract abnormalities that would indicate CNS involvement. Musculoskeletal injury was also reported in recent Wuhan reports. Related muscle symptoms and injury were reported to be accompanied by marked elevation in creatine kinase and lactate dehydrogenase levels. This injury could be associated with ACE2 expression in the musculoskeletal system, but the ACE2 receptor cannot be detected through autopsy sampling; therefore, further studies are required. However, a systemic immune response induced by infection may cause damage to skeletal muscle, as indicated by marked increases in proinflammatory cytokine levels in serum.

Therapeutics

Current Drug Therapies for COVID-19

The lopinavir and ritonavir are HIV type I asparate protease inhibitors that have been found to be potent against SARS-CoV-2 in vitro. In a recent randomized, controlled, open-label trial involving hospitalized adult patients with confirmed SARS-CoV-2 infection, the benefits of lopinavir and ritonavir treatment compared with standard care were not confirmed. Remdesivir, a nucleotide analog prodrug that inhibits viral replicase, was initially developed for Ebola virus and demonstrated efficacy in reducing the virus load in MERS-CoV in non-human primates. A recent report on the application of remdesivir in patients with severe COVID-19 reported 68% clinical improvement in the need for oxygen support. Although the mortality rate reached 18%, it was lower than that in a previous study that reported mortality rates of 22% and 66% (44 of 67) among patients receiving invasive mechanical ventilation. The anti-influenza drug favipiravir (Avigan) has also demonstrated some promising effects. In a recent open-labelled randomized study, patients treated with favipiravir demonstrated quicker recovery from fever and cough but similar rates of respiratory failure compared with a control group receiving umifenovir. Hydroxychloroquine and chloroquine have demonstrated the ability to inhibit SARS-CoV-2 in vitro. Although treatment with hydroxychloroquine and azithromycin was significantly associated with decreased viral load in a small trial in France, the therapeutic effect remains questionable because it failed to eliminate the virus or significantly relieve symptoms in a recent randomized controlled trial conducted in China. Finally, tocilizumab, a humanized monoclonal antibody against the IL-6 receptor that was traditionally used to treat patients with rheumatoid arthritis, has also been approved for use in China.

3.2. Drug Precautions for Patients With Stroke

Notably, immunomodulatory agents such as tocilizumab increase the risk of opportunistic infections. Cardiac toxicity, including long QT syndrome and conduction abnormalities, is a notable effect of hydroxychloroquine and chloroquine application. Tocilizumab and other IL-6 receptor antagonists may also increase CV risk by inducing unfavorable changes in lipid profiles. The continued use of ACE and angiotensin-receptor blockers is still suggested because switching to another medication incurs a higher risk than that associated with infection, especially for hypertension management in patients with stroke.

Neurorehabilitation Therapy Could Potentially Be Taught and Practiced at Home

Because physical therapy and rehabilitation are inaccessible resources during pandemics, neurorehabilitation often cannot be offered to patients with stroke on the same scale as it can during pandemic-free conditions, especially during the acute and subacute phases; consequently, patients may be prevented from reaching the optimal recovery phase. Studies have indicated that prolonged immobility among patients with stroke may result in significant functional decline. Thus, some strategies for facilitating neurorehabilitation may be applied in the absence of assistance from physical and occupational therapists. Several potential techniques can be used to stimulate neurorestoration and maintain muscle strength with minimal assistance; these are listed as follows.

Portable Transcutaneous Electrical Stimulation Device

Transcutaneous electrical stimulation (TENS) devices use different current and frequency parameters to stimulate sensory and peripheral nerves. Electrical sensory input can contribute to routine rehabilitation and improve early poststroke lower-extremity impairment.
and late motor function. Several studies have shown that TENS can maintain muscle strength and mass in a deconditioned state. Such devices are safe and easy to use. In hemiplegic limbs, where the muscle groups are flaccid, proper selection of the stimulation site significantly improves the flaccid limb. Poststroke spasticity in lower limbs can be effectively reduced by TENS when applied for more than 30 minutes over a nerve or muscle belly in patients with chronic stroke. In addition, peripheral nerve stimulation at ulnar and radial sites for 1 h has been revealed to increase corticomotor function and improve hand dexterity in patients with moderate to severe hemiparesis. Thus, TENS may be utilized as a convenient tool for temporal function and muscle facilitation to maintain therapeutic effects with the provision of proper assistance. Prolonged periods of sensory stimulation, such as TENS combined with activity, can have beneficial effects for treating impaired function after stroke.

**Mirror Therapy**

Mirror therapy (MT) has been proven to be an effective and feasible approach for rehabilitating patients who have had a stroke. MT utilizes a mirror that reflects the movement of an unaffected limb and gives the illusion of movement of the affected limb. This visual stimulus is believed to facilitate the mirror neurons involved in imitative learning through interaction with the neural motor area. MT was also reported to ameliorate an imbalance in function of the cortical excitability hemisphere. MT was found to confer a significant positive effect on motor function when applied for 15 to 60 min per session over the course of 2 to 8 weeks. The application time is adjustable to acute, subacute, and chronic cases of stroke. The mirror is normally positioned between the affected and unaffected limbs such that the movement of the healthy limb is perceived as the movement of the unaffected limb. The entire procedure is straightforward to execute through simple instruction and can be performed under minimal supervision.

**Home Exercise Programs**

Increasing evidence suggests that the implementation of home-based exercise is noninferior to outpatient courses. Home-based locomotion training with physical therapists can achieve the target response with the same efficiency as outpatient courses among patients with stroke. Mayo et al found that combined cycle and supervised walking training at home successfully improved patient’s long-term walking ability. Although most home-based exercise programs must be supervised by a therapist, some exercises can be performed smoothly with assistance from properly instructed family members.

**Virtual Reality Exercise**

The application of virtual reality (VR) is increasingly being used in stroke rehabilitation. Several studies have demonstrated that VR technology can improve motor functioning. VR can also be used to improve upper limb function, gait and balance, global motor function, and cognitive function in patients with stroke. However, VR equipment is usually expensive and complex and may only be available in specialist hospitals. The Nintendo Wii system supplemented with a balance board and a bar enabling body movement in a VR game environment could be a viable option for use in treatment for patients with stroke. It was shown to be useful as an adjunct therapy to traditional treatment in improving dynamic balance in patients who have had a stroke.

**Conclusion**

The COVID-19 pandemic has not only had a direct impact on people’s health but also has greatly influenced public access to hospitals, which may prevent patients who have had a stroke from receiving standard rehabilitation therapy. In this review, we summarize the neurological manifestations of COVID-19 described in the accumulating reports that may lead to neurological complications in patients with stroke. The ACE2 receptor is crucial in viral transmission, but it is still not recommended that patients stop using ACE or angiotensin-receptor–blocker drugs essential for hypertension control. For the current choice in anti-COVID19 medication, we advise practitioners to be aware of the cardiovascular or infection risks associated with hydroxychloroquine or immunomodulatory agents such as tocilizumab. Portable devices such as TENS devices can be easily used to maintain muscle strength and reduce spasticity at home when access to hospitals is limited. A combination of basic home exercises with VR implemented by video game consoles such as Wii may also be a feasible technique for maintaining physical balance and protecting functional deterioration.

**Funding**

This work was financially supported by Taipei Veterans General Hospital, Yuli branch (VHYL-108-01), Ministry of Science and Technology (108-2314-B-010-042-MY3) and Taipei Veterans General Hospital-National Yang-Ming University Excellent Physician Scientists Cultivation Program No. 108-V-B-008.

**Disclosure of interest**

The authors have no competing interests to declare.
References

1. Mao L, Jin H, Wang M, et al. Neurologic manifestations of hospitalized patients with Coronavirus disease 2019 in Wuhan, China. JAMA Neurol 2020.

2. Oxley TJ, Mocco J, Majidi S, et al. Large-vessel stroke as a presenting feature of Covid-19 in the young. N Engl J Med 2020;e60.

3. Preliminary estimates of the prevalence of selected underlying health conditions among patients with Coronavirus Disease 2019—United States, February 12-March 28, 2020. MMWR Morb Mortal Wkly Rep 2020;69(13):382-386.

4. Mehra MR, Desai SS, Kuy S, Henry TD, Patel AN. Cardiovascular disease, drug therapy, and mortality in Covid-19. N Engl J Med 2020.

5. Yang X, Yu Y, Xu J, 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.

6. Belouzard S, Millet JK, Licitra BN, Whittaker GR. Mechanisms of coronavirus cell entry mediated by the viral spike protein. Viruses 2012;4(6):1011-1033.

7. Chen Y, Liu Q, Guo D. Emerging coronaviruses: genome structure, replication, and pathogenesis. J Med Virol 2020;92(4):418-423.

8. Lan J, Ge J, Yu J, et al. Structure of the SARS-CoV-2 spike receptor-binding domain bound to the ACE2 receptor. Nature 2020.

9. Di Gennaro F, Pizzol D, Marotta C, et al. Coronavirus diseases (COVID-19) current status and future perspectives: a narrative review. Int J Environ Res Public Health 2020;17(8).

10. Tu YF, Chien CS, Yarmishyn AA, et al. A Review of SARS-CoV-2 and the Ongoing Clinical Trials. Int J Mol Sci 2020;21(7).

11. Prompetchara E, Ketloy C, Palaga T. Immune responses in COVID-19 and potential vaccines: Lessons learned from SARS and MERS epidemic. Asian Pac J Allergy Immunol 2020;38(1):1-9.

12. Rose-John S. Interleukin-6 Family Cytokines. Cold Spring Harb Perspect Biol 2018;10(2).

13. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet (London, England) 2020;395(10223):497-506.

14. Oudkerk M, Builler HR, Kuipers D, et al. Diagnosis, prevention, and treatment of thromboembolic complications in COVID-19: report of the national institute for public health of the Netherlands. Radiology 2020;201629.

15. Magro C, Mulvey JJ, Berlin D, et al. Complement associated microvascular injury and thrombosis in the pathogenesis of severe COVID-19 infection: a report of five cases. Transl Res J Lab Clin Med 2020.

16. Grillet F, Behr J, Calame P, Aubry S, Delabrousse E. Acute pulmonary embolism associated with COVID-19 Pneumonia detected by pulmonary CT angiography. Radiology 2020;201544.

17. Oudkerk M, Builler HR, Kuipers D, et al. Diagnosis, prevention, and treatment of thromboembolic complications in COVID-19: report of the national institute for public health of the Netherlands. Radiology 2020;201629.

18. Abiodun OA, Ola MS. Role of brain renin angiotensin system in neurodegeneration: an update. Saudi J Biol Sci 2020;27(3):905-912.

19. Divani AA, Andalib S, Di Napoli M, et al. Coronavirus disease 2019 and stroke: clinical manifestations and pathophysiological insights. J Stroke Cerebrovasc Dis 2020;29(8):104941.

20. Arroja MM, Reid E, McCabe C. Therapeutic potential of the renin angiotensin system in ischaemic stroke. Exp Transl Stroke Med 2016;8:8.

21. Wang K, Chen W, Zhou Y-S, et al. SARS-CoV-2 invades host cells via a novel route: CD147-spike protein. Biorxiv 2020. 2020.2003.2014.988345.

22. Devaux CA, Rolain J-M, Colson P, Raoult D. New insights on the antiviral effects of chloroquine against coronavirus: what to expect for COVID-19. Int J Antimicrob Agents 2020;55(5):105938.

23. Ghebriali M, Wang K, Viveiros A, et al. Angiotensin Converting Enzyme 2: SARS-CoV-2 Receptor and Regulator of the Renin-Angiotensin System. Circ Res 2020.

24. Bennion DM, Haltigan E, Regenhardt RW, Steckelings UM, Sumners C. Neuroprotective mechanisms of the ACE2-angiotensin-(1-7)-Mas axis in stroke. Curr Hypertens Rep 2015;17(2):3.

25. Regenhardt RW, Bennion DM, Sumners C. Cerebroprotective action of angiotensin peptides in stroke. Clin Sci (Lond) 2014;126(3):195-205.

26. Mogi M, Kawajiri M, Tsukuda K, Matsumoto S, Yamada T, Horiiuchi M. Serum levels of renin-angiotensin system components in acute stroke patients. Geriatr Gerontol Int 2014;14(4):793-798.

27. Vaduganathan M, Vardeny O, Michel T, McMurray JJV, Pfeffer MA, Solomon SD. Renin-Angiotensin-Aldosterone System Inhibitors in Patients with Covid-19. N Engl J Med 2020.

28. Danzi GB, Loffi M, Galeazzi G, Gherbesi E. Acute pulmonary embolism and COVID-19 pneumonia: a random association. Eur Heart J 2020.

29. Ishiguro T, Matsu K, Fuji S, Takayanagi N. Acute thrombotic vascular events complicating influenza-associated pneumonia. Respir Med Case Rep 2019;28:100884.

30. Arachchilage DRJ, Laffan M. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. J Thromb Haemost : JTH 2020;18(5):1233-1234.

31. Tang N, Bai H, Chen X, Gong J, Li D, Sun Z. Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. J Thromb Haemost : JTH 2020;18(5):1094-1099.

32. Wang D, Hu B, Hu C, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel Coronavirus-infected Pneumonia in Wuhan, China. JAMA 2020;323(11):1061-1069.

33. Han H, Yang L, Liu R, et al. Prominent changes in blood coagulation of patients with SARS-CoV-2 infection. Clin Chem Lab Med 2020;58(7):1116-1120.

34. Ding Y, Wang H, Shen H, et al. The clinical pathology of severe acute respiratory syndrome (SARS): a report from China. J Pathol 2003;200(3):282-289.

35. Umaphati T, Kor AC, Venkatsubramanian N, et al. Large artery ischaemic stroke in severe acute respiratory syndrome (SARS). J Neurol 2004;251(10):1227-1231.

36. Eliezer M, Hautefort C, Hamel AL, et al. Sudden and complete olfactory loss function as a possible symptom of COVID-19. JAMA Otolaryngol-Head Neck Surg 2020.

37. Cabello-Verrugio C, Morales MG, Rivera JC, Cabrera D, Simon F. Renin-angiotensin system: an old player with
38. Ding Y, He L, Zhang Q, et al. Organ distribution of severe acute respiratory syndrome (SARS) associated coronavirus (SARS-CoV) in SARS patients: implications for pathogenesis and virus transmission pathways. J Pathol 2004;203 (2):622-630.

39. Chu CM, Cheng VCC, Hung IFN, et al. Role of lopinavir/ritonavir in the treatment of SARS: initial virological and clinical findings. Thorax 2004;59(3):252-256.

40. Chen F, Chan KH, Jiang Y, et al. In vitro susceptibility of 10 clinical isolates of SARS coronavirus to selected antiviral compounds. J Clin Virol 2004;31(1):69-75.

41. Cao B, Wang Y, Wen D, et al. A trial of lopinavir-ritonavir in adults hospitalized with severe Covid-19. N Engl J Med 2020.

42. Callaway E, Cyparoski D, Mallapaty S, Stoye E, Tollefson J. The coronavirus pandemic in five powerful charts. Nature 2020;579(7800):482-483.

43. Grein J, Ohmagari N, Shin D, et al. Compassionate use of remdesivir for patients with severe Covid-19. N Engl J Med 2020.

44. Wu C, Chen X, Cai Y, et al. Risk Factors associated with acute respiratory distress syndrome and death in patients with Coronavirus disease 2019 Pneumonia in Wuhan, China. JAMA Intern. Med. 2020.

45. Chen C, Zhang Y, Huang J, et al. Favipiravir versus Arbidol for COVID-19: a randomized clinical trial. MedRxiv 2020. 2020.2003.20037432.

46. Wang M, Cao R, Zhang L, et al. Remdesivir and chloroquine effectively inhibited the recently emerging novel coronavirus (2019-nCoV) in vitro. Cell Res 2020;30(3):269-271.

47. Yao X, Ye F, Zhang M, et al. In vitro antiviral activity and projection of optimized dosing design of hydroxychloroquine for the treatment of severe acute respiratory syndrome Coronavirus 2 (SARS-CoV-2). Clin Infect Dis : Off Publ Infect Dis Soc Am 2020.

48. Gautret P, Lagier JC, Parola P, et al. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. Int J Antimicrob Agents 2020;109(49).

49. Tang W, Cao Z, Han M, et al. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label, randomized, controlled trial. MedRxiv 2020. 2020.2004.2010.2006058.

50. Zhang Q, Wang Y, Qi C, Shen L, Li J. Clinical trial analysis of 2019-nCoV therapy registered in China. J Med Virol 2020.

51. Rutherford AJ, Subasinghe S, Hrych KL, Galloway JB. Serious infection across biologic-treated patients with rheumatoid arthritis: results from the British society for Rheumatology biologics register for Rheumatoid Arthritis. Ann Rheum Dis 2018;77(6):905-910.

52. Chatre C, Roubille F, Vernhet H, Jorgensen C, Pers YM. Cardiac complications attributed to chloroquine and hydroxychloroquine: a systematic review of the literature. Drug Saf 2018;41(10):919-931.

53. Lentini G, Cavalluzzi MM, Habtemariam S. COVID-19, Chloroquine repurposing, and cardiac safety concern: chirality might help. Molecules 2020;25(8).

54. Xie F, Yun H, Levitan EB, Muntner P, Curtis JR. Tocilizumab and the risk of cardiovascular disease: direct comparison among biologic disease-modifying antirheumatic drugs for rheumatoid arthritis patients. Arthritis Care Res 2019;71(8):1004-1018.

55. Fievet P, Gregoire J, Agnes E, et al. Renin-angiotensin-aldosterone system, urinary prostaglandins and kaliuretic effect in pregnancy-induced hypertension: evidence for a dysregulation of the renin-angiotensin-prostaglandin loop. J Hypertens Suppl 1986;4(5):S88-591.

56. McInlchey MP, James J, McKevitt C, Douiri A, McChlaining S, Sackley CM. The effect of rehabilitation interventions on physical function and immobility-related complications in severe stroke: a systematic review. Syst Rev 2018;7(1):197.

57. Sharififar S, Shuster JJ, Bishop MD. Adding electrical stimulation during standard rehabilitation after stroke to improve motor function, a systematic review and meta-analysis. Ann Phys Rehabil Med 2018;61(5):339-344.

58. Jung KS, In TS, Cho HY. Effects of sit-to-stand training combined with transcutaneous electrical stimulation on spasticity, muscle strength and balance ability in patients with stroke: a randomized controlled study. Gait Posture 2017;54:183-187.

59. Mahmoud A, Veluswamy SK, Hombali A, Mullick A, N M, Solomon JM. Effect of transcutaneous electrical nerve stimulation on spasticity in adults with stroke: a systematic review and meta-analysis. Arch Phys Med Rehabil 2019;100(4):751-768.

60. Liu J, Au-Yeung SYY. Corticomotor excitability effects of peripheral nerve electrical stimulation to the paretic arm in stroke. Am J Phys Med Rehabil 2017;96(10):687-693.

61. Gandhi DB, Sterba A, Khatter H, Pandian JD. Mirror therapy in stroke rehabilitation: current perspectives. Ther Clin Risk Manage 2020;16:75-85.

62. Carvalho D, Teixeira S, Lucas M, et al. The mirror neuron system in post-stroke rehabilitation. Int Arch Med 2013;6 (1):41.

63. Thieme H, Morkisch N, Mehrholz J, et al. Mirror therapy for improving motor function after stroke. Cochrane Database Syst Rev 2018;7:CD008449.

64. Mayo NE. Stroke Rehabilitation at Home: Lessons Learned and Ways Forward. Stroke 2016;47(6):1685-1691.

65. Duncan PW, Sullivan KJ, Behrmann AL, et al. Bodyweight-supported treadmill rehabilitation after stroke. N Engl J Med 2011;364(21):2026-2036.

66. Mayo NE, MacKay-Lyons MJ, Scott SC, Morriello C, Brophy J. A randomized trial of two home-based exercise programmes to improve functional walking post-stroke. Clin Rehabil 2013;27(7):659-671.

67. In T, Lee K, Song C. Virtual Reality Reflection Therapy Improves Balance and Gait in Patients with Chronic Stroke: Randomized Controlled Trials. Med Sci Monit : Int Med J Exp Clin Res 2016;22:4046-4053.

68. Mekbib DB, Han J, Zhang L, et al. Virtual reality therapy for upper limb rehabilitation in patients with stroke: a meta-analysis of randomized clinical trials. Brain Inj 2020;34(4):456-465.

69. Laver KE, Lange B, George S, Deutsch JE, Saposnik G, Crotty M. Virtual reality for stroke rehabilitation. Cochrane Database Syst Rev 2017;11:CD008349.

70. Karasu AU, Batur EB, Karatas GK. Effectiveness of Wii-based rehabilitation in stroke: a randomized controlled study. J Rehabil Med 2018;50(5):406-412.