Long Term Covid-19 Syndrome in Non-Hospitalized Patient a Cross-Sectional Study

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Abstract

Introduction: COVID-19 exposes patients to new, recurrent, or ongoing conditions that affect their health. Patients experience different symptoms that can last beyond 12 weeks after first being infected with COVID- 19 (Post Covid-19 syndrome). Even the acutely asymptomatic patients later developed Post Covid-19 syndrome. These circumstances can present as diverse types or combinations of health problems for different lengths of time.

Methods: This is a cross-sectional study of 217 SARS-CoV-2 laboratory-positive patients (SARS-CoV-2+) between March 2020 and July 2021. Inclusion criteria: all patients 18 years and older with a previous diagnosis of COVID-19. Charts were reviewed to find patients with persistent problems after a COVID-19 infection or new diagnosis during the acute infection that persisted or appeared 12 weeks after having a SARS-CoV-2 positive test. Also, we designed a population-based survey to assess the persistence of the symptoms. No protected health information was collected, and verbal consent obtained.

Results: Of 217 patients included in the study, the median age was 68 years old, and the most common long terms effects of COVID-19 were anosmia and ageusia at 15.7% followed by dyspnea with 7.8%. Depression was diagnosed in 6% of patients. Cardiopulmonary, neurologic, and gastrointestinal symptoms were also found to be present in several patients.

Conclusions: COVID-19 may cause multiorgan system impairment with many survivors experiencing cardiovascular, respiratory, neurological, psychiatric, and gastrointestinal system compromise.

Keywords: Long Term COVID-19 Effect; Complication; SARS-Cov-2; Anosmia; Ageusia; Dyspnea; Depression

Introduction

Coronaviruses are one of the most prevalent human and animal pathogens. At the end of 2019, a novel coronavirus was identified as the cause of a cluster of pneumonia cases in Wuhan, a city in the Hubei Province of China. As this novel coronavirus spread, it resulted in an epidemic through China, which led to a rapidly increasing number of cases internationally. The virus that causes COVID-19 is designated as a severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2); previously, it was referred to as 2019-nCoV [1]. The spectrum of symptomatic infection ranges from mild to critical, with more infections being mild [2]. While most infections are minor, some require hospitalization. In a study that included 2741 patients who were hospitalized for COVID-19 in a New York City health care system, 24%, died or were discharged to hospice. 60% of the patients who received invasive mechanical ventilation died, 13% were still ventilated and 16% were discharged by the end of the study [3].

There is a misconception that patients with COVID-19 recover within a couple of weeks, but this is not always the case. There is no absolute definition of post-Covid-19 syndrome. It is believed to be an illness among patients who have recovered from Covid-19 but still

have ongoing symptoms or symptoms lasting longer than normally expected. Long-term consequences of COVID-19 have been determined by the CDC as they refer to the long-term symptoms people may experience after recovering from the disease. As the world is still fighting against the COVID-19 pandemic, it is still early to determine the full picture of the long-term complications of this devastating disease [4].

Several symptoms that have been reported which include; fatigue shortness of breath, cough, joint pain, myalgia, brain fog, headache, anosmia and hypogeusia, dizziness, palpitations, chest pain, depression or anxiety, fever, multiorgan effects like multisystem inflammatory syndrome (MIS) [4-6].

These long-term complications are sometimes referred to as Long COVID-19 or long-haul COVID-19 [7]. This category of patients represented about 10% of people according to WHO report and there is a growing concern over it [8]. As some countries recover and others are still suffering from the devastating COVID pandemic crisis, the COVID consequences might be considered as another public health crisis [9,10].

The presence of symptoms beyond 3 weeks from the initial onset of symptoms is currently defined as post-acute COVID-19, while chronic COVID-19 can be defined as extending the symptoms beyond 12 weeks [11]. The post-acute COVID-19 syndrome is observed among patients who had severe illness, as well as it has been reported by patients who had milder form of the disease [12,13]. Another notable complication is the community acquired pneumonia which requires multiple outpatient physician visits became more prominent among COVID-19 long-haul [14]. Because of the wide variety of the post COVID-19 symptoms, the need for an interdisciplinary approach has been emphasized [15].

We present a cross-sectional study on the prevalence of the long-term complications of COVID 19 from 217 patients that were seropositive for COVID 19.

Manifestations

The results of an 8-month follow-up study showed that 26% seropositive vs 9% seronegative reported at least 1 moderate to severe symptom lasting for at least 2 months (RR, 2.9 [95% CI, 2.2 - 3.8]) and 15% vs 3% reported at least 1 moderate to severe symptom lasting for at least 8 months (RR, 4.4 [95% CI, 2.9 - 6.7]). In the seropositive group, the most common moderate to severe symptoms (for at least 2 months) were anosmia, fatigue, ageusia, and dyspnea. 2-15% of the participants of the study reported their long-term symptoms moderately to markedly disrupted their work, social, and home life [16].

Another 2 months follow up study showed that only 12.6% were completely free of any COVID-19-related symptoms, while 32% had 1 or 2 symptoms and 55% had 3 or more. None of the patients had fever or any signs or symptoms of acute illness during follow up. Worsened quality of life was observed among 44.1% of patients. The commonly reported symptoms were fatigue (53.1%), dyspnea (43.4%), joint pain, (27.3%) and chest pain (21.7%) [5].

Cardiovascular [Chest pain, shortness of breath, Palpitations, fatigue]

A cardiovascular magnetic resonance imaging follow-up for patients recently recovered from COVID-19 revealed that the most prevalent abnormality was myocardial inflammation (defined as abnormal native T1 and T2 measures) [6,17]. A notable change has been detected in (60%) of patients recently recovered from COVID-19, followed by regional scar and pericardial enhancement. "Viral Sepsis" believed to be the factor behind the observed changes, which was associated with significant rise of troponin T levels and diffuse cardiac inflammation [18,19]. Cardiac viral sepsis might be the underlying cause of the long-term consequences of COVID-19 [6,20], including significantly reduced ejection fraction, dyspnea, and chest pain [5,21].

Pulmonary [shortness of breath, cough, Chest pain]

Completely recovered COVID-19 patients have been followed-up for 3 months after discharge has shown that (64%) had persistent symptoms and (71%) had radiologic abnormalities consistent with pulmonary dysfunction [13]. Pulmonary fibrosis and evidence of interstitial thickening were the prominent findings [22].

In (75%) of the recovered patients after 3 months, pulmonary function tests changes have been observed. These changes included: decline in FEV1/FVC ratio, decreased diffusion capacity for carbon monoxide (DLCO) [15.5 - 43.6% of patients], reduced lung volumes (TLC, RV and VC), diminished respiratory muscle strength [50% of patients] and a shorter 6-minute walking distance (6MWD) test. Global concerns are raised regarding the assessment of lung injury for discharged COVID-19 patients [23].

Neurologic, Cognitive and Psychiatric [brain fog, headache, Anosmia, Hypogeusia, dizziness, hearing loss, bell's palsy, depression, or anxiety]

The most reported long-term neurologic symptoms after COVID-19 are headache, vertigo, and chemosensory dysfunction as anosmia and ageusia [13]. It is believed that the viremia associated with COVID-19 has a penetrating capacity to the brain tissue, leading to endothelial dysfunction. Also, it might be due to direct invasion of the olfactory nerve through trans synaptic spread [24,25].

Although grave consequences such as stroke, encephalitis, seizures, and other conditions such as major mood swings and "brain fog" have been reported up to 2 to 3 months after initial illness onset, all have been reported as uncommon [24,26].

Headaches can affect up to one-third of diagnosed patients, but prevalence varies in different reports. It was found in 21 clinical studies and 8 meta-analyses that the frequency of headache associated with COVID-19 was 5.6% to 70.3% of cases [24,27].

Anosmia and Ageusia (chemosensory dysfunction) are also reported among the COVID-19 patients with a prevalence of 5.6% hypogeusia, 5.1% hyposmia [28], and 19.4% - 88.0% reported another chemosensory dysfunction [24,29,30].

There have only been a few cases reported of sudden onset sensorineural hearing loss in patients with no previous otologic problems and their only current medical condition at the time of sudden hearing loss was the diagnosis of Sars-Cov-2. In all cases there was no clear etiology, but it is significant to consider COVID-19 as the possible causative agent as it binds to the ACE-2 receptor found in the auditory canal [31-33]. In patients with sudden onset sensorineural hearing loss, cell injury is induced by the release of cytokines and increase inflammation processes. Histopathology of the disease presents with loss of hairy cells without infiltration suggesting the pathology to be related with a stress process [34].

Facial nerve palsy, also known as Bell's palsy, is the most common facial nerve paralysis around the world, and it is also idiopathic in most cases [35]. China reported the first cases of Bell's palsy in patients with Covid-19 [36], and after that; around the world, more cases had been reported and an association between SARS-CoV2 and Bell's palsy has been suggested. At least 24% of patients who present to the ER with facial nerve paralysis were currently infected or recently infected with SARS-CoV2 [37,38]. The emotional, behavioral, and mental health consequences associated with COVID-19 might be due to the stress and social distancing resulting from the pandemic [13,40]. A list of COVID-19 related cognitive consequences may range from feelings of isolation and loneliness to depression, anxiety, posttraumatic stress disorder (PTSD), and substance use disorder [13]. A 4-month study revealed that symptoms of anxiety were found in 31% of patients and symptoms of depression in 21% [41]. An overall survey revealed cognitive and neurologic symptoms in 16% to 23% of the participated COVID-19 recovered patients [42]. The prevalence of neuropsychiatric symptoms is not yet determined and needs further studies.

Gastrointestinal symptoms (nausea, vomiting or diarrhea)

COVID-19 causes upregulation of inflammatory mediators such as cytokines and serotonin which affects the Gut-Brain Axis [43]. The dysfunction of the Gut-Brain Axis could play a role in the irritable bowel and the functional dyspepsia following recovery from COVID-19 infection [44]

Recovered COVID-19 patients suffering from COVID-19 related GI complications account for a large subset of COVID-19 recovered patients according to a study of national healthcare databases from the US Department of Veterans Affairs, looked at over 73,000 patients. The study identified a significant increase in GI related diagnoses as esophageal diseases, abdominal pain, diarrhea, and irritable bowel syndrome, as well as increased use of laxatives, histamine receptor antagonists, and acid-suppressive medicines [45].

The GI symptoms have been reported among COVID-19 cases and they had significantly higher rates of other associated symptoms such as fever >38.5°C (39.19%), fatigue (31.08%), shortness of breath (10.81%) and headache (21.62%) (46). Diarrhea was the most notable GI symptom, but other symptoms such as nausea, vomiting, and abdominal pain sometimes preceded the respiratory symptoms, and sometimes as the only symptoms related to the course of COVID-19 [47]. Although the COVID-19 is well known as a respiratory virus, its fecal-oral transmission could be a turning point in its management [48], because the angiotensin-converting enzyme 2 receptor site is present both in the respiratory tract and in the enterocytes of the GI tract [49,50].

Alongside the above-mentioned symptoms, various degrees of liver injury have been reported in COVID-19 patients [51,52]. Despite the liver chemistry abnormalities and Cholangiopathy seen in COVID-19 patients, they are usually transient and resolve with disease resolution [53].

Methods

This is a cross - sectional study of 217 SARS-CoV-2 laboratory-positive patients (SARS-CoV-2+) between March 2020 and July 2021. We are interested to know the long-term effects of Covid defined as the persistence of Covid-19 related symptoms beyond 12 weeks [54]. Charts were reviewed to find patients with persistent problems after a COVID-19 infection or new diagnosis during the acute infection that persisted or appeared 12 weeks after having a SARS-CoV-2 positive test. Also, we designed a population-based survey to assess the persistence of the symptoms. No protected health information was collected, and verbal consent obtained.

Subject selection

Inclusion criteria

To be included in the study population, patients will have to be 18 years of age or older and be diagnosed with SARS-CoV-2+ confirmed by SARS-CoV-2 PCR in swab or sputum.

Exclusion criteria

Patients were excluded if they were younger than 18 years old, or if they never had a diagnosis of SARS-CoV-2.

Results

The population described in this study consisted of 217 patients above the age of 18 years old with a median age of 68. The results of the study are presented in figure 1. Almost half of the patients were presented with a long-term effect from COVID 19. The most common presentation of long term COVID was anosmia and agnosia at 15.7% of the cases followed by dyspnea with 7.8%. New onset Major Depressive Disorder was diagnosed in 6% of patients with PHQ-9.
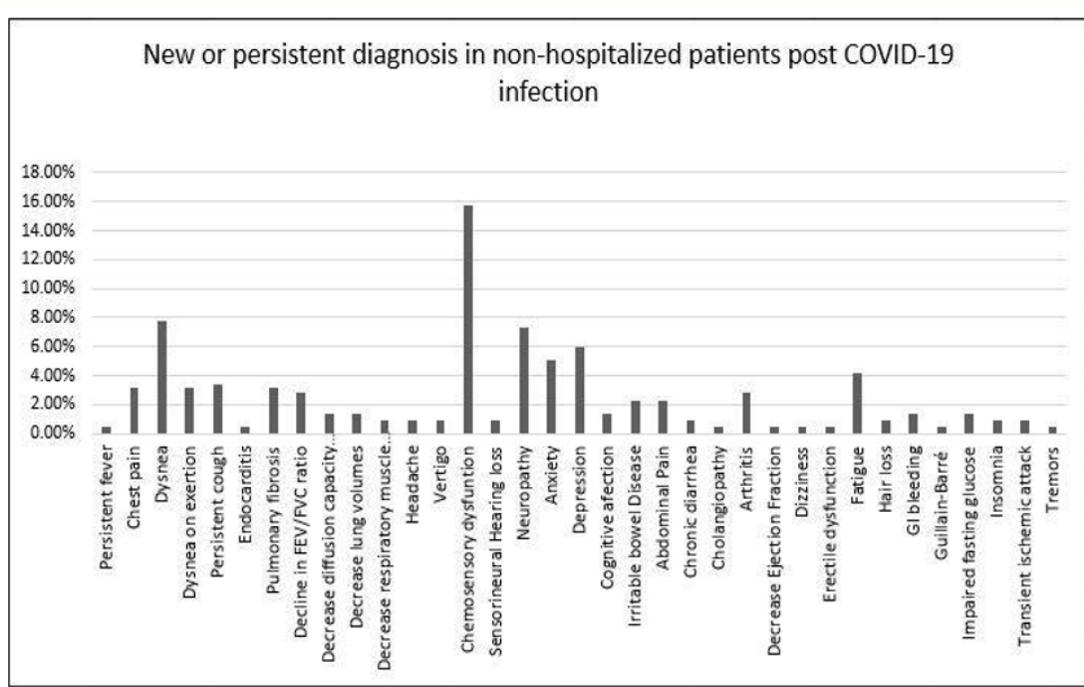
Figure 1: New or persistent diagnosis in non-hospitalized patients post COVID-19 infection. 2020-2021.

The cardiopulmonary manifestations reported were chest pain, persistent cough, dyspnea on exertion, and pulmonary fibrosis at 3.2% each. One of the cases was a report of cardiac viral sepsis. Decline in FEV/VC ratio, diffusion capacity of CO, decrease in lung volumes and respiratory muscle strength was noted in some patients that presented comparative pulmonary function tests from prior studies.

The neurologic manifestations found were the chemosensory dysfunction already described. A total of 16 patients were presented with polyneuropathy or mononeuropathy. Two patients developed vertigo and persistent headaches were reported in another two patients. There were also two cases of sensorineural hearing loss reported and a particular case of Guillain-Barre Syndrome.

Cognitive function was affected in 1.4% of patients and the psychiatric affections most reported were depression in 6% and anxiety in 5% of cases.

The most common gastrointestinal manifestations reported were irritable bowel disease and abdominal pain with five patients each. There were three patients with Gastrointestinal bleeding and cholangiopathy was found in one of the cases reported.

Other systemic manifestations found in the study were arthritic exacerbations in 2.3% of patients. Fatigue was reported in 4.1% of cases.

There were single cases of; atelectasis, decrease in ejection fraction, dizziness, erectile dysfunction, hair loss, insomnia, Left Bundle Branch Block, restless leg syndrome, pleural effusion, and transient ischemic attack.

Conclusion

The novel SARS-CoV-2 leading to COVID-19 has affected billions of individuals and caused over 30 million deaths worldwide [55]. COVID-19 is known for its effects on the respiratory system but reports of lasting symptoms in other organ systems are rising.

Clinicians should be aware that over the next upcoming months to years, there will be a rise in post-COVID-19 functional disorders, involving different systems and it should be included in the list of differential diagnosis. Patients to be considered at elevated risk of Post Covid-19 symptoms should not only include those who had proven COVID-19 by diagnostic testing, but those who also may have had COVID-19-related symptoms but never underwent diagnostic testing due to only experiencing vague symptoms not typical to the presentation of this infection.

COVID-19 can affect multiple systems including; cardiovascular, respiratory, neurologic, psychiatric, and gastrointestinal organs. At this moment of research, it is imperative to continue adequate patient follow-up, to allow for future longitudinal observational studies that will allow us to early aim at potential future treatment to help prevent the long-term effects of Covid.

The complete evidence of the involvement of SARS-CoV2 in the neurologic system and the recent neurotropic enrolment of the virus described in its genome [56,57], suggest the need of attention of these manifestations as they can also be one of the primary cause of deaths and complicate late manifestations in different organs of the body.

Covid-19 vaccines are considered the first line of defense to reduce the cases of the ongoing pandemic [39]. The late manifestations of COVID-19 should be followed up in all patients exposed to the virus (symptomatic and asymptomatic) and, the entire population who have received the vaccine.

One thing remains true and is that the fight against this virus is not over, and the ongoing battle requires us to use what we have available -the vaccine- and continue to carefully review the risk-benefit of lifting restrictions to prevent careless transmission. We will have to rely on the data available thus far and will require more research to understand why some of these stubborn symptoms persist like described in our study. We hope this study can enlighten the path to further studies and future meta-analysis which seem premature at this time.

Bibliography

1. WHO Director-General's opening remarks at the media briefing on COVID-19 - 11 (2020).

2. Abdullah F., *et al*. "Decreased severity of disease during the first global omicron variant covid-19 outbreak in a large hospital in tshwane, south Africa". *The International Journal of Infectious Diseases* 116 (2022): 38-42.

3. Petrilli CM., *et al*. "Factors associated with hospital admission and critical illness among 5279 people with coronavirus disease 2019 in New York City: prospective cohort study". *British Medical Journal* 22 (2020): 369.

4. Post-COVID Conditions | CDC (2021).

5. Carfi A., *et al*. "Persistent symptoms in patients after acute COVID-19". *JAMA - Journal of the American Medical Association. American Medical Association* 324 (2020): 603-605.

6. Puntmann VO., *et al*. "Outcomes of Cardiovascular Magnetic Resonance Imaging in Patients Recently Recovered from Coronavirus Disease 2019 (COVID-19)". *JAMA Cardiology* 5.11 (2020): 1265-1273.

7. What It Means to Be a Coronavirus "Long-Hauler" – Health Essentials from Cleveland Clinic (2021).

8. Zoller M., *et al*. Coronavirus disease Der Anaesthesist 69 (2020).

9. Long-Haul COVID-19 May Be a Public Health Crisis After the Pandemic (2021).

10. Rubin R. "As Their Numbers Grow, COVID-19 "Long Haulers" Stump Experts". *The Journal of the American Medical Association* 324.14 (2020): 1381-1383.

11. Greenhalgh T., *et al*. "Management of post-acute covid-19 in primary care". *British Medical Journal* 11 (2020): 370.

12. Tenforde MW., *et al*. "Symptom Duration and Risk Factors for Delayed Return to Usual Health Among Outpatients with COVID-19 in a Multistate Health Care Systems Network - United States, March–June 2020". *Morbidity and Mortality Weekly Report* 69.30 (2020): 993-998.

13. Del Rio C., *et al*. "Long-term Health Consequences of COVID-19". *JAMA - Journal of the American Medical Association American Medical Association* 324 (2020): 1723-1724.

14. Metlay JP., *et al*. "Measuring symptomatic and functional recovery in patients with community-acquired pneumonia". *Journal of General Internal Medicine* 12.7 (1997): 423-430.

15. Landi F., *et al*. "Post-COVID-19 global health strategies: the need for an interdisciplinary approach". *Aging Clinical and Experimental Research* 32.8 (2020): 1613-1620.

16. Havervall S., *et al*. "Symptoms and Functional Impairment Assessed 8 Months after Mild COVID-19 among Health Care Workers". *JAMA - Journal of the American Medical Association American Medical Association* 325 (2021): 2015-2016.

17. Shi S., *et al*. "Association of Cardiac Injury with Mortality in Hospitalized Patients with COVID-19 in Wuhan, China". *JAMA Cardiology* 5.7 (2020): 802-810.

18. Li H., *et al*. "SARS-CoV-2 and viral sepsis: observations and hypotheses". *The Lancet* 395 (2020): 1517-1520.

19. Kindermann I., *et al*. "Predictors of outcome in patients with suspected myocarditis". *Circulation* 118.6 (2008): 639-648.

20. Grn S., *et al*. "Long-term follow-up of biopsy-proven viral myocarditis: Predictors of mortality and incomplete recovery". *Journal of the American College of Cardiology* 59.18 (2012): 1604-1615.

21. Rajpal S., *et al*. "Cardiovascular Magnetic Resonance Findings in Competitive Athletes Recovering from COVID-19 Infection". *JAMA Cardiology American Medical Association* 6 (2021): 116-118.

22. Zhao Y miao., *et al*. "Follow-up study of the pulmonary function and related physiological characteristics of COVID-19 survivors three months after recovery". *EClinical Medicine* 25 (2020): 100463.

23. Huang Y., *et al*. "Impact of coronavirus disease 2019 on pulmonary function in early convalescence phase". *Respiratory Research BioMed Central* 21 (2020): 163.

24. Zubair AS., *et al*. "Neuropathogenesis and neurologic manifestations of the coronaviruses in the age of coronavirus disease 2019: A review". *JAMA Neurology American Medical Association* 77 (2020): 1018-1027.

25. Nauen DW., *et al*. "Assessing Brain Capillaries in Coronavirus Disease 2019". *JAMA Neurology* 78.6 (2021): 760-762.

26. Pennisi M., *et al*. "Sars-cov-2, and the nervous system: From clinical features to molecular mechanisms". *International Journal of Molecular Sciences* 21 (2020): 1-21.

27. Suzuki K. "Coronavirus disease 2019 (COVID-19) and headaches". *Journal of Clinical Neurology* 60.9 (2020): 589-596.

28. Mao L., *et al*. "Neurologic Manifestations of Hospitalized Patients with Coronavirus Disease 2019 in Wuhan, China". *JAMA Neurology* 77.6 (2020): 683-690.

29. Vaira LA., *et al*. "Anosmia and Ageusia: Common Findings in COVID-19 Patients". *Laryngoscope* 130.7 (2020): 1787.

30. Lechien JR., *et al*. "Olfactory and gustatory dysfunctions as a clinical presentation of mild-to-moderate forms of the coronavirus disease (COVID-19): a multicenter European study". *European Archives of Oto-Rhino-Laryngology* 277.8 (2020): 2251-2261.

31. Koumpa FS., *et al*. "Sudden irreversible hearing loss post COVID-19". *BMJ Case Reports* 13.11 (2020).

32. Degen C., *et al*. "Acute Profound Sensorineural Hearing Loss After COVID-19 Pneumonia". *Mayo Clinic Proceedings* 95 (2020): 1801-1803.

33. Kalcioglu MT., *et al*. "Can COVID-19 cause sudden sensorineural hearing loss?" *International Journal of Infectious Diseases* 101 (2020): 205.

34. Merchant SN., *et al*. "Pathology and pathophysiology of idiopathic sudden sensorineural hearing loss". *Otology and Neurotology* 26.2 (2005): 15-160.

35. Heckmann JG., *et al*. The Diagnosis and Treatment of Idiopathic Facial Paresis (Bell's Palsy) (2019).

36. Wan Y., *et al*. Coronavirus disease 2019 complicated with Bell's palsy: a case report (2020): 1-7.

37. Codeluppi L., *et al*. "Facial palsy during the COVID-19 pandemic". *Brain and Behavior* 11.1 (2021).

38. Islamoglu Y., *et al*. "Facial paralysis as the only symptom of COVID-19: A prospective study". *American Journal of Otolaryngology and Head and Neck Surgery* 42.4 (2021): 102956.

39. Soeiro T., *et al*. "Type I interferons as the potential mechanism linking mRNA COVID-19 vaccines to Bell's palsy". *Therapies* (2021): 5-6.

40. Galea S., *et al*. "The Mental Health Consequences of COVID-19 and Physical Distancing: The Need for Prevention and Early Intervention". *JAMA Internal Medicine. American Medical Association* 180 (2020): 817-818.

41. Morin L., *et al*. "Four-Month Clinical Status of a Cohort of Patients after Hospitalization for COVID-19". *JAMA - Journal of the American Medical Association American Medical Association* 325.15 (2021): 1525-1534.

42. Prescott HC. "Outcomes for Patients following Hospitalization for COVID-19". *JAMA - Journal of the American Medical Association American Medical Association* 325 (2021): 1511-1512.

43. Margolis KG., *et al*. "The Microbiota-Gut-Brain Axis: From Motility to Mood". *Gastroenterology* 160 (2021): 1486-1501.

44. Gurusamy SR., *et al*. "Small Intestinal Bacterial Overgrowth in Functional Dyspepsia: A Systematic Review and Meta-Analysis". *The American Journal of Gastroenterology* 116.5 (2021): 935-942.

45. Al-Aly Z., *et al*. "High-dimensional characterization of post-acute sequelae of COVID-19". *Nature* 594.7862 (2021): 259-264.

46. Jin X., *et al*. "Epidemiological, clinical and virological characteristics of 74 cases of coronavirus-infected disease 2019 (COVID-19) with gastrointestinal symptoms". *Gut* 69.6 (2020): 1002-1009.

47. Post-COVID-19 GI Symptoms: Are We in for the Long Haul? (2021).

48. Kaźmierczak-Siedlecka K., *et al*. "COVID-19 – Gastrointestinal and gut microbiota-related aspects". *European Review for Medical and Pharmacological Sciences* 24.20 (2020): 10853-10859.

49. Xiao F., *et al*. "Evidence for Gastrointestinal Infection of SARS-CoV-2". *Gastroenterology* 158.6 (2020): 1831-1833.

50. Marasco G., *et al*. "Implications of SARS-CoV-2 infection for neurogastroenterology". *Neurogastroenterology and Motility* 33 (2021).

51. Mohandas S and Vairappan B. "Severe acute respiratory syndrome coronavirus-2 infection and the gut–liver axis". *Journal of Digestive Diseases* 21 (2020): 687-695.

52. Cha MH., *et al*. "Gastrointestinal and hepatic manifestations of COVID-19: A comprehensive review". *World Journal of Gastroenterology* 26 (2020): 2323-2332.

53. Roth NC., *et al*. "Post–COVID-19 Cholangiopathy: A Novel Entity". *The American Journal of Gastroenterology* 116.5 (2021): 1077-1082.

54. Fernández-De-las-peñas C., *et al*. "Defining post-covid symptoms (post-acute covid, long covid, persistent post-covid): An integrative classification". *International Journal of Environmental Research and Public Health* 18 (2021): 1-9.

55. COVID-19 Map - Johns Hopkins Coronavirus Resource Center (2021).

56. Zhou Z., *et al*. "Understanding the neurotropic characteristics of SARS-CoV-2: from neurological manifestations of COVID-19 to potential neurotropic mechanisms". *Journal of Neurology* 267 (2020): 2179-2184.

57. Li YC., *et al*. "The neuroinvasive potential of SARS-CoV2 may play a role in the respiratory failure of COVID-19 patients". *Journal of Medical Virology* 92 (2020): 552-555.

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