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Research Article

An Insight in to Post-Covid Syndrome in Covid-19 Long Haulers

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Abstract:

Background: Post-COVID syndrome includes a spectrum of symptoms that occur after COVID-19. It has a plethora of symptoms ranging from neuropsychiatric symptoms to dermatologic symptoms thereby affecting the quality of life of COVID-19 long haulers. There are no evidence-based international guidelines to follow for the management of post-COVID syndrome and thus it remains a clinical issue.

Objectives: To study about the post-COVID syndrome and its effect on COVID-19 long haulers.

Methodology: The recent studies related to the aim of the review were undertaken through a literature search to study in detail about post-COVID syndrome.

Results: Post-COVID syndrome can be classified into different types according to the initial symptoms, time of initiation, duration of symptoms, and period of quiescence. Females are at higher risk of developing this syndrome. Fatigue is the most common symptom of post-COVID syndrome and can persist for several months. It can be diagnosed through history collection, physical examination and blood tests. A positive COVID-19 test cannot be considered as a diagnostic test for post-COVID syndrome. Inflammatory response occurs and inflammatory cytokines are release in huge amount leading to cytokine storm. Cytokine storm may lead to the development of acute respiratory distress syndrome and a phase of long drawn immunosuppression. Light aerobic exercises, breathing exercises, complementary behavioural modification and psychological support may help in improving the condition of the individuals. There are no evidence-based international guidelines to follow for the management of post-COVID syndrome and thus it remains a clinical issue.

Conclusion: Post-COVID syndrome is a new and distinct phenomenon. It mostly remains unclear regarding the long-term effects of COVID-19, but researchers are working. However, its symptoms, could have far-reaching consequences for a person's quality of life, affecting personal life and their career goals.

Keywords: COVID-19, respiratory distress, cytokine storm, dyspnea, sepsis

1. INTRODUCTION

COVID-19 is caused by the severe acute respiratory syndrome coronavirus 2, a new coronavirus (SARS-CoV-2 or 2019-nCoV). The first case of COVID-19 was reported in December 2019 in Wuhan, China ¹. According to WHO, 186 million cases and almost 4 million deaths had been reported as of July 11, 2021 ². The clinical course of SARS-CoV-2 infections can range from asymptomatic infection to respiratory disease, multi-organ failure, and death. The intensity of the ailment is connected to the infected persons' age and comorbidities; the elderly people are particularly impacted, necessitating ICU treatment ³.

Pneumonia, acute respiratory distress syndrome (ARDS), sepsis, multiple organ failure, blood coagulation, myocarditis, acute myocardial infarction, acute kidney injury, and other viral and bacterial infections that are not unique to coronavirus can all result in serious consequences ^{4,5}. COVID-19-related death is thought to be caused by pneumonia and cytokine storm syndrome-related hyperinflammation. One of the most prevalent symptoms of SARS-CoV-2 is interstitial pneumonia, which can be worsened by acute respiratory distress syndrome, a disease associated with a high death rate, particularly in elderly persons with numerous comorbidities ⁶.

Anosmia/ageusia, fever, dry cough, shortness of breath, exhaustion, myalgias, nausea/vomiting or diarrhoea, headache, weakness, rhinorrhea are all symptoms of COVID-19. Lymphopenia and raised inflammatory markers (e.g., erythrocyte sedimentation rate, C-reactive protein, ferritin, tumour necrosis factor-, IL-1, and IL-6) are among the laboratory abnormalities ^{7,8}. COVID-19 causes severe problems, including cardiac, brain, lung, hepatic, renal, and coagulation system dysfunction ⁹. Supportive treatment such as antibiotics, vitamins, trace elements, and antipyretics, seems to be the only option for mild cases. Oxygen therapy, with or without

mechanical ventilation, should be begun and customised for people with respiratory distress ¹⁰. Many drugs have been tested in clinical trials to see if they can act as antivirals, but no definite data have been found to show that any of the medications researched had a verified effect ¹¹. In extreme cases, corticosteroids as an anti-inflammatory may be necessary in addition to symptomatic treatment ¹².

It is a common misperception that all COVID-19 patients would cure in two weeks; however, this is not always the case. A significant number of people infected with SARS-CoV-2 continue to experience symptoms long after they have recovered from the earliest stages of COVID-19 disease ¹³. COVID-19 infection has long-term implications that are unknown. Furthermore, even in patients with moderate symptoms who did not require hospitalisation, extended symptoms recovery have been reported. This symptom was called "long COVID" or "post-COVID syndrome" ¹⁴. Post-COVID lasts longer than three weeks after the onset of symptoms. Irrespective of comorbidities, it is predicted that 10% to 35% of patients who do not require hospitalisation develop post-COVID symptoms with rates as high as 80% recorded among hospitalised patients and patients with severe diseases. Because many persons were never tested for COVID-19, a positive test is not required for diagnosis of post-acute or chronic illness ⁸.

Hence the current study aims to investigate the post-COVID manifestation.

2. RESULTS AND DISCUSSION

1.1 Classification of post-COVID syndrome:

There are five categories of protracted COVID-19 syndrome, according to the University of Cincinnati Medical Centre's recommended criteria for COVID-19 sequelae based on initial symptoms, time of start, duration of symptoms, and period of quiescence: Type 1 patients have a recovery time that is specifically linked to the

severity of the acute infection, organ complications, and underlying medical conditions; Type 2 is defined by symptoms lasting six weeks after the onset of illness; Type 3 is defined by a period of quiescence or near-complete recovery followed by a recurrence of symptoms lasting at least three months (Type 3A) or at least six months (Type 3B); Type 4 is characterised by patients who are initially asymptomatic at the time of a positive SARS-CoV-2 test but become symptomatic one to three months after the test is positive (Type 4A) or at least three months later. Type 5 patients are asymptomatic or have few symptoms at the time of diagnosis and die within the next 12 months ¹⁵.

1.2 Risk factors:

Female gender, extended recovery, sustained positivity on RT-PCR (Reverse transcriptase-polymerase chain reaction) after day 14 of the first test, moderate or severe sickness at presentation, respiratory distress, drowsiness, and previous psychiatric problem are all associated with an increased risk of developing post-COVID symptoms. All the age groups are equally vulnerable to developing post-COVID syndrome ^{16,17}.

1.3 Clinical spectrum:

Symptoms of post-acute COVID-19 are diverse. Even so-called mild COVID-19 can cause long-term symptoms like as cough, low-grade fever, and lethargy, which can all return and remit. Fatigue is the most prevalent post-COVID symptom, with rates ranging from 17.5 percent to 72 percent among hospitalised patients. It can last for up to seven months after the onset of illness and cause severe disability ¹⁸.

Dyspnea, chest pain, muscle pains and weakness, metabolic disruption (such as poor diabetes control), neurocognitive difficulties, headaches, gastrointestinal upset, thromboembolic conditions, rashes, depression and other mental health conditions are among the other symptoms reported ¹⁹.

1.3.1 Pulmonary symptoms:

Dyspnea and impaired exercise tolerance were recorded in 10–40% of hospitalised COVID-19 patients for 2–4 months following discharge, while 65.6 percent of patients admitted to the intensive care unit (ICU) had new or worsening dyspnea ²⁰. Residual dyspnea persisted in around 10% and 40% of COVID-19 survivors who reported having it during the acute phase of the disease, respectively, two and four months ²¹.

1.3.2 Dermatologic symptoms:

Hair loss is the most common symptom, with around 20% of COVID-19 survivors reporting it. Rashes on the skin, such as vesicular, maculopapular, urticarial, or chilblain-like lesions on the extremities, can also occur (so called covid toe) ²².

1.3.3 Neuropsychiatric symptoms:

Even six months following COVID-19, sleep and mental issues such as anxiety and depression may impact roughly 26% and 40% of patients, respectively ²³. Manifestations may include obsession and compulsion, reduced social activity, poor concentration, aggression, irritability, substance use, and cognitive deficit ²⁴. After recovery from a life-threatening illness, such as COVID-19, post-traumatic stress disorder, a mental condition generated by life-stressing causes, may arise; according to recent studies, the prevalence rate may range from 5.8 percent to 43 percent ²⁵. COVID-19 survivors have described prolonged malaise, diffuse myalgia, depressed symptoms, and non-restorative sleep as a post-viral syndrome. Migraine-like headaches are another post-acute symptom of COVID-19. In about one-tenth of patients at up to 6 months follow-up, loss of smell and taste may continue following resolution of other symptoms ²⁶. Brain fog, which can show as issues with focus, memory, receptive language, and/or executive function, has been observed with or without fluctuations ²⁷.

Novel neurological symptoms have been reported as a result of this neuroinflammatory disorder, including cerebrovascular disorders such as cerebral vasculitis, haemorrhage and ischemic stroke^{28,29}. Altered mental status (e.g., myoclonus, encephalopathy, encephalitis, seizure), peripheral nervous system involvement (e.g., myositis, Guillain-Barre syndrome), and neuropsychiatric involvement (e.g., depression) As a post-COVID consequence, acute transverse myelitis has also been reported³⁰.

1.3.4 Cardiovascular symptoms:

Post-COVID has also been linked to heart damage. In a radiographic investigation of 100 COVID-19 patients who had been discharged, cardiac anomalies and myocardial inflammation were observed in 78 percent and 60 percent of the participants, respectively, which were not related to the severity of COVID-19 at the time of discharge³¹. In another study, 46 percent of 26 athletes with asymptomatic SARS-CoV-2 infection also had cardiac inflammation³². Radiological anomalies of ventricular remodelling were present in 29 percent of 79 COVID-19 survivors three months after discharge³³. Cardiovascular symptoms such as chest discomfort, palpitations, and tachycardia might last up to six months in COVID-19 survivors³⁴.

1.3.5 Gastrointestinal symptoms:

Although the incidence of gastrointestinal symptoms varies depending on study design, meta-analyses have suggested that 10–20 percent of COVID-19 patients experience gastrointestinal symptoms (such as nausea, diarrhoea, poor appetite, vomiting and abdominal irritation)³⁵. Patients with COVID-19 experienced gut microbiome disruption (i.e., gut dysbiosis), which lasted for at least 10 days and up to 30 days following disease cure³⁶.

1.3.6 Renal symptoms:

Acute kidney injury (AKI) requiring renal replacement treatment (RRT) arises in 5% of all

hospitalised patients and 20–31% of critically ill patients with acute COVID-19, diagnosed with severe infections needing artificial respiration. Early trials with short-term follow-up in RRT patients found that 27–64 percent were dialysis-free by 28 days or ICU discharge. In the post-acute COVID-19 Chinese study, 35 percent of patients had lower estimated glomerular filtration rate (eGFR; defined as 90ml per min per 1.73m²) at 6 months, and 13 percent had new-onset drop of eGFR following verified normal renal function during acute COVID-19. With adequate longer-term follow-up data, those patients who require RRT for severe AKI experience high mortality, and rates of renal recovery reportedly at 84% among survivors³⁷⁻³⁹.

1.3.7 Endocrine symptoms:

Individuals without diabetes mellitus have developed diabetic ketoacidosis weeks or even months after COVID-19 symptoms have resolved⁴⁰. Likewise, weeks after the remission of respiratory symptoms, subacute thyroiditis with clinical thyrotoxicosis has been reported⁴¹. COVID-19 may potentially exacerbate latent thyroid autoimmunity, such as Hashimoto's thyroiditis or Graves' disease⁴².

1.3.8 Hematologic symptoms:

A single-centre study of 163 patients without post-discharge thromboprophylaxis in the United States found a 2.5 percent cumulative incidence of thrombosis 30 days after discharge, including segmental pulmonary embolism, intracardiac thrombus, thrombosed arteriovenous fistula, and ischemic stroke⁴³. At 30 days after discharge, there was a 3.7 percent cumulative incidence of bleeding, largely due to mechanical falls. In retrospective studies from the United Kingdom similar venous thromboembolism rates were observed^{44,45}.

1.3.9 General symptoms:

Tiredness is the most common symptom of post-COVID syndrome with rates ranging from 17.5

percent to substantially greater percentages (up to 60.3 and 72.0 percent respectively) among hospitalised COVID-19 patients in wards or critical care units ²⁵. Recovery of olfactory and gustatory dysfunction can take more than a month following the onset of taste and smell loss with up to 11% and 9% of patients affected beyond six months post-hospital release, respectively ⁴⁶.

1.4 Post-COVID mechanism:

An immense and lengthy counterbalancing compensatory anti-inflammatory response syndrome (CARS) occurs following trauma or a severe primary infectious disease like COVID-19, in which a systemic inflammatory response syndrome (SIRS) is prominent, leading to postinfectious/posttraumatic immunosuppression ⁴⁷. The CARS response, an exact duplicate counterpoise to SIRS or systemic inflammatory response syndrome, is designed to reduce proinflammation, avoid maladaptive multiple-organ dysfunction, and regulate the restoration to immunologic homeostasis ⁴⁸. Various continuously interacting and conflicting variables are at work in COVID-19, orchestrating a finely regulated balance of pro- and anti-inflammatory responses, i.e., SIRS and CARS, that ultimately determines the result. Increased inflammatory responses are characterized by an increased release of inflammatory cytokines such as interleukins 1, 6, 8, 17, and 1, monocyte chemoattractant protein-1, and tissue necrosis factor, collectively referred as “cytokine storm” ⁴⁹. They are a feature of viral exposure or inoculum, the presence/absence of comorbidities, and the state of immunocompetence. If left unchecked, acute lung injury (ALI), acute respiratory distress syndrome (ARDS), coagulopathy, hypotension, hypoperfusion, organ failure (also known as multiple-organ failure or multiple-organ dysfunction) and death can happen ⁵⁰. Conceding that the inflammatory response is suppressed too far in the direction of CARS, the patient, having “weathered” the initial hyper inflammatory cytokine storm and development to ARDS, could lead to a phase of long drawn

immunosuppression known as PICS (persistent inflammation, immunosuppression, and catabolism syndrome), that is seen after sepsis and is one of the most common causes of death ²⁴.

1.5 Diagnosis:

After a thorough history and physical examination, blood tests should be conducted deliberately and for particular clinical indications. In the case of a gasping patient, anaemia should be ruled out. A symptom of serious, acute COVID-19 is lymphopenia. C reactive protein, white cell count, natriuretic peptides, ferritin, troponin and D-dimer are all examples of increased biomarkers ³. Screening for troponin and D-dimer may be mistakenly positive, although a negative result might help to alleviate clinical confusion. Further research is likely to refine the indications for, and interpretation of, diagnostic and monitoring tests in follow-up of covid-19. The British Thoracic Society's guidance on follow-up of COVID-19 patients who have had a major respiratory problem recommends community follow-up with a chest x-ray at 12 weeks and transfer for new, lasting, or advancing complaints for individuals who were not hospitalised to critical care ³³.

1.6 Lifestyle modifications:

The literature thus far has only suggested that rehabilitation may work for treating certain cases of long COVID but it should be personalized since long COVID manifestation and pathophysiology may vary in each case. In rehabilitation, patients are advised to perform light aerobic exercise paced according to individual capacity. Exercise difficulty levels are increased gradually within tolerated levels until improvements in fatigue and dyspnoea are seen, typically four to six weeks. Rehabilitation also includes breathing exercises that aim to control slow, deep breaths to strengthen respiratory muscles' efficiency, especially the diaphragm. The breath should be inhaled through the nose, expanding the abdominal region, and exhaled via the mouth. Such light aerobic and breathing

exercises should be performed daily in 5–10 min sessions throughout the day. Complementary behavioural modification and psychological support may also help improve survivors' well-being and mental health¹⁵. In an observational study of 23 discharged COVID-19 patients with on-going symptoms, a personalized multidisciplinary rehabilitation approach involving breathing, mobilisation, and psychological interventions have improved lung function and physical capacity. However, most participants' lung function did not heal completely, and persistent neurological symptoms remained. Risks of physical rehabilitation must also be considered. Even though rehabilitation helps in certain COVID-19 cases, it may not be suitable for survivors of critical COVID-19 with severe pulmonary or cardiac damage⁵¹.

1.7 Management:

Patients with post-COVID syndrome should be managed pragmatically and symptomatically to minimise over investigation. Serious consequences as well as other possible causes of persistent symptoms should be ruled out. New or worsening symptoms should be investigated because they could suggest long-term consequences like heart problems or pneumonia. A chest radiograph at 12 weeks should be explored for patients who have had substantial respiratory disease. Blood tests, electrocardiogram, chest radiograph and urine tests can help determine the reason of persistent symptoms and rule out major conditions like pulmonary embolism and myocarditis, even though they aren't usually essential¹⁵.

Management of post-COVID syndrome remains a clinical issue because, there are no evidence-based international guidelines to follow. Anticoagulation is used to treat a pulmonary embolism for at least three months. There is no agreement on the effectiveness or duration of post-discharge prophylaxis with low molecular weight heparin. The treatment of COVID-19-induced pulmonary fibrosis is similarly unknown.

Clinical, radiological, and biochemical indicators are needed to help doctors predict which COVID-19-related ARDS patients are likely to develop pulmonary fibrosis once COVID-19 is resolved⁵².

3. CONCLUSION:

Post-COVID syndrome is a new and distinct phenomenon. It mostly remains unclear regarding the long-term effects of COVID-19, but researchers are working. However, its symptoms, could have far-reaching consequences for a person's quality of life, affecting personal life and their career goals. Clinicians should regularly keep a check on persons who have undergone COVID-19 to evaluate how their systems perform once they have recovered. It is vital to keep in mind that most COVID-19 patients recover rapidly. However, because of the long-term consequences of COVID-19, it is even more critical to prevent COVID-19 from spreading by taking safeguards like wearing masks, maintaining social distancing and taking vaccines.

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REFERENCES:

1. Zhou P, Yang XL, Wang XG, Hu B, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. *Nature*. 2020; 579(7798): 270-273.
2. World Health Organization. Weekly Epidemiological Update on COVID-19-13 July 2021. <http://www.who.int/publications/m/item/weekly-epidemiological-update-on-covid-19---13-july-2021>. Published July 13, 2021. Accessed August 8, 2021.
3. Kingstone T, Taylor AK, O'Donnell CA, Atherton H, Blane DN, Chew GCA. Finding the 'right' GP: a qualitative study

- of the experiences of people with long-COVID. *Br J Gen Pract.* 2020; 4(5): 1-12.
4. Rodriguez MAJ, Cardona OJA, Gutierrez OE, et al. Clinical, laboratory and imaging features of COVID-19: a systematic review and meta-analysis. *Travel Med Infect Dis.* 2020; 34: 101623.
 5. Zheng KI, Feng G, Liu WY, Targher G, Byrne CD, Zheng MH. Extrapulmonary complications of COVID-19: A multisystem disease? *J Med Virol.* 2020; 93(1): 323-335.
 6. Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ. COVID-19: consider cytokine storm syndromes and immunosuppression. *Lancet.* 2020; 395 (10229): 1033–1034.
 7. Mao R, Qiu Y, He JS, Tan JY, Li XH, Liang J, et al. Manifestations and prognosis of gastrointestinal and liver involvement in patients with COVID19: a systematic review and meta-analysis. *Lancet Gastroenterol Hepatol.* 2020; 5(7): 667–678.
 8. Levi M, Thachil J, Iba T, Levy JH. Coagulation abnormalities and thrombosis in patients with COVID-19. *Lancet Haematol.* 2020; 7(6): 438–440.
 9. Long B, Brady WJ, Koyfman A, Gottlieb M. Cardiovascular complications in COVID-19. *Am J Emerg Med.* 2020; 38(7): 1504–1507.
 10. Li T, Lu H, Zhang W. Clinical observation and management of COVID-19 patients. *Emerg Microbes Infect.* 2020; 9(1): 687-690.
 11. Gao J, Tian Z, Yang X. Breakthrough: Chloroquine phosphate has shown apparent efficacy in treatment of COVID-19 associated pneumonia in clinical studies. *Biosci Trends.* 2020; 14(1): 72-73.
 12. Fadel R, Morrison AR, Vahia A, et al. Early Short Course Corticosteroids in Hospitalized Patients with COVID-19. *Clin Infect Dis.* 2020; 71(16): 2114-2120.
 13. Misra DP, Agarwal V, Gasparyan AY, Zimba O. Rheumatologists' perspective on coronavirus disease 19 (COVID-19) and potential therapeutic targets. *Clin Rheumatol.* 2020; 39(7): 2055-2062.
 14. Greenhalgh T, Knight M, A'Court C, Buxton M, Husain L. Management of post-acute COVID-19 in primary care. *Br Med J.* 2020; 370: m3026.
 15. Becker RC. COVID-19 and its sequelae: A platform for optimal patient care, discovery and training. *J Thromb Thrombolysis.* 2021; 1–8.
 16. Mahmud R, Rahman MM, Rassel MA, et al. Post-COVID-19 syndrome among symptomatic COVID-19 patients: A prospective cohort study in a tertiary care center of Bangladesh. *PLoS ONE.* 2021; 16(4): e0249644.
 17. Poyraz BC, Poyraz CA, Qlgun Y, et al. Psychiatric morbidity and protracted symptoms after COVID-19. *Psychiatry Res.* 2020; 295: 113604.
 18. Havervall S, Rosell A, Phillipson M, et al. Symptoms and functional impairment assessed 8 months after mild COVID-19 among health care workers. *J Am Med Assoc.* 2021; 325(19): 2015-2016.
 19. Dasgupta A, Kalhan A, Kalra S. Long term complications and rehabilitation of COVID-19 patients. *J Pak Med Assoc.* 2020; 70(5): S131-135.
 20. Halpin SJ, McIvor C, Whyatt EG, et al. Post-discharge symptoms and rehabilitation needs in survivors of COVID-19 infection: A cross-sectional evaluation. *J Med Virol.* 2021; 93(2): 1013–1022.
 21. Davis HE, Assaf GS, McCorkell L, et al. Characterizing Long COVID in an International Cohort: 7 Months of Symptoms and Their Impact. *E Clin Med.* 2021; 101019: 1-19.
 22. Galvan CC, Catala A, Carretero HG, et al. Classification of the cutaneous manifestations of COVID-19: a rapid

- prospective nationwide consensus study in Spain with 375 cases. *Br J Dermatol.* 2020; 183(1): 71-77.
23. Huang C, Huang L, Wang Y, et al. 6-month consequences of COVID-19 in patients discharged from hospital: A cohort study. *Lancet.* 2021; 397(10270): 220–232.
 24. Bellan M, Soddu D, Balbo PE, et al. Respiratory and psychophysical sequelae among patients with COVID-19 four months after hospital discharge. *J Am Med Assoc Netw Open.* 2021; 4(1): e2036142.
 25. Simani L, Ramezani M, Darazam IA. Prevalence and correlates of chronic fatigue syndrome and post-traumatic stress disorder after the outbreak of the COVID-19. *J Neurovirol.* 2021; 27: 154–159.
 26. Belvis R. Headaches during COVID-19: my clinical case and review of the literature. *Headache.* 2020; 60(7): 1422–1426.
 27. Heneka MT, Golenbock D, Latz E, Morgan D, Brown R. Immediate and long-term consequences of COVID-19 infections for the development of neurological disease. *Alzheimers Res Ther.* 2020; 12(1): 69.
 28. Raahimi MM, Kane A, Moore CE, et al. Late onset of Guillain-Barre syndrome following SARS-CoV-2 infection: part of ‘long COVID-19 syndrome’?. *Br Med J Case Rep.* 2021; 14(1): e240178.
 29. Camdessanche JP, Morel J, Pozzetto B, et al. COVID-19 may induce Guillain-Barré syndrome. *Rev Neurol (Paris).* 2020; 176(6): 516–518.
 30. Emamikhah M, Babadi M, Mehrabani M, et al. Opsoclonusmyoclonus syndrome, a post-infectious neurologic complication of COVID-19: case series and review of literature. *J Neurovirol.* 2021; 1–9.
 31. Puntmann VO, Carerj ML, Wieters I, et al. Outcomes of cardiovascular magnetic resonance imaging in patients recently recovered from Coronavirus Disease 2019 (COVID-19). *J Am Med Assoc Cardiol.* 2020; 5(11): 1265–1273.
 32. Rajpal S, Tong MS, Borchers J, et al. Cardiovascular magnetic resonance findings in competitive athletes recovering from COVID-19 infection. *J Am Med Assoc Cardiol.* 2020; 6(1): 116–118.
 33. Moody WE, Liu B, Mahmoud-Elsayed HM, et al. Persisting Adverse Ventricular Remodeling in COVID-19 Survivors: A Longitudinal Echocardiographic Study. *J Am Soc Echocardiogr.* 2021; 34(5): 562–566.
 34. Carfi A, Bernabei R, Landi F. Gemelli Against COVID-19 Post-Acute Care Study Group. Persistent symptoms in patients after acute COVID-19. *J Am Med Assoc.* 2020; 324(6): 603–605.
 35. Cheung KS, Hung IFN, Chan PPY, et al. Gastrointestinal manifestations of SARS-CoV-2 infection and virus load in fecal samples from a Hong Kong Cohort: systematic review and meta-analysis. *Gastroenterol.* 2020; 159(1): 81–95.
 36. Yeoh YK, Zuo T, Lui GCY, et al. Gut microbiota composition reflects disease severity and dysfunctional immune responses in patients with COVID-19. *Gut.* 2021; 70(4): 698–706.
 37. Robbins JSY, Long Q, Kristen LK, et al. Outcomes for patients with COVID-19 and acute kidney injury: a systematic review and meta-analysis. *Kidney Int Rep.* 2020; 5(8): 1149–1160.
 38. Cummings MJ, Baldwin MR, Abrams D, et al. Epidemiology, clinical course, and outcomes of critically ill adults with COVID-19 in New York City: a prospective cohort study. *Lancet.* 2020; 395(10239): 1763–1770.
 39. Gupta S, Hayek SS, Wang W, et al. Factors associated with death in critically ill patients with coronavirus disease 2019 in the US. *J Am Med Assoc Intern Med.* 2020; 180(11): 1436-1447.

40. Suwanwongse K, Shabarek N. Newly diagnosed diabetes mellitus, DKA, and COVID-19: causality or coincidence? A report of three cases. *J Med Virol.* 2021; 93(2): 1150-1153.
41. Ruggeri RM, Campenni A, Siracusa M, Frazzetto G, Gullo D. Subacute thyroiditis in a patient infected with SARS-COV-2: an endocrine complication linked to the COVID-19 pandemic. *Hormones (Athens).* 2021; 20(1): 219–221.
42. Tee LY, Hajanto S, Rosario BH. COVID-19 complicated by Hashimoto's thyroiditis. *Singapore Med J.* 2020; 62(5): 265.
43. Patell R, Bogue T, Koshy A, et al. Post-discharge thrombosis and hemorrhage in patients with COVID-19. *Blood.* 2020; 136(11): 1342–1346.
44. Roberts LN, Whyte MB, Georgiou L, et al. Post-discharge venous thromboembolism following hospital admission with COVID-19. *Blood.* 136(11): 1347–1350.
45. Salisbury R, Iotchkova V, Jaafar S, et al. Incidence of symptomatic, image-confirmed venous thromboembolism following hospitalization for COVID-19 with 90-day follow-up. *Blood Adv.* 2020; 4(24): 6230–6239.
46. Addison AB, Wong B, Ahmed T, et al. Clinical Olfactory Working Group Consensus Statement on the Treatment of Post Infectious Olfactory Dysfunction. *J Allergy Clin Immunol.* 2021; 147(5): 1704-1719.
47. Hotchkiss RS, Monneret G, Payen D. Sepsis-induced immunosuppression: from cellular dysfunctions to immunotherapy. *Nat Rev Immunol.* 2013; 13: 862–874.
48. Bone RC. Sir Isaac Newton, sepsis, SIRS, and CARS. *Critical Care Medicine.* 24(7): 1125–1128.
49. Bozza FA, Salluh JJ, Japiassu AM. Cytokine profiles as markers of disease severity in sepsis: a multiplex analysis. *Crit Care.* 2007; 11(2): R49.
50. Kell DB, Pretorius E. To what extent are the terminal stages of sepsis, septic shock, systemic inflammatory response syndrome, and multiple organ dysfunction syndrome actually driven by a prion/amyloid form of fibrin?. *Semin Thromb Hemost.* 2018; 44(3): 224–238.
51. Puchner B, Sahanic S, Kirchmair R, et al. Beneficial effects of multi-disciplinary rehabilitation in post-acute COVID-19 – an observational cohort study. *Eur J Phys Rehabil Med.* 2021; 57(2): 189–198.
52. Vasarmidi E, Tsitoura E, Spandidos DA, Tzanakis N, Antoniou KM. Pulmonary fibrosis in the aftermath of the COVID-19 era (Review). *Exp Ther Med.* 2020; 20(3): 2557-2560.