World Journal of Advanced Pharmaceutical and Life Sciences

Journal homepage: https://zealjournals.com/wjapls/

ISSN: 2799-0222 (Online)

(REVIEW ARTICLE)

Check for updates

Long COVID: An unpredicted multisystem syndrome of COVID-19 disease

SHITAL VISHNU PATIL [1,*], NEEL TANDEL [2] and GAJANAN GODHALI [3]

[1] *Associate Professor& Head, Pulmonary Medicine, MIMSR Medical college, & Venkatesh Hospital, Latur, Maharashtra, India*
[2] *Junior Resident, Radiodiagnosis, MIMSR Medical college, Latur, Maharashtra, India*
[3] *Associate Professor, Internal Medicine, MIMSR Medical college, Latur, Maharashtra, India*

World Journal of Advanced Pharmaceutical and Life Sciences, 2023, 04(01), 005–012

Publication history: Received on 04 January 2023; revised on 18 February 2023; accepted on 21 February 2023

Article DOI: https://doi.org/10.53346/wjapls.2023.4.1.0054

Abstract

Long COVID is multisystem syndrome with nonspecific symptoms and organic signs of unidentified pathology occurs after COVID-19 disease. Long COVID symptoms has been documented in some cases irrespective of disease severity or hospitalization. Long COVID symptoms has significant impact on quality of life in those cases suffered from disease in recent past and lingering to almost two years since infection. Importantly, not all cases of COVID-19 were shown long COVID symptoms. Pathophysiology resulting into long COVID manifestations is still not completely validated. Researchers have reported 'immune dysregulation' and 'coagulation abnormalities' are probable pathophysiological mechanism for long COVID. Some of the long COVID effects shown complete reversibility including post COVID lung fibrosis. Reboot system to restore immune dysregulation and recovery in long COVID is real concern. Vaccination has not shown significant effect modifying long COVID manifestation.

Keywords: Long COVID; COVID-19; Coagulation abnormalities; Immune dysregulation

1. Introduction

"Long COVID" is a term used to describe presence of various symptoms, even weeks or months after acquiring SARS-CoV-2 infection irrespective of the viral status. It is also called "post-COVID syndrome". It can be continuous or relapsing and remitting in nature. There can be the persistence of one or more symptoms of acute COVID, or appearance of new symptoms. Majority of people with post-COVID syndrome are PCR negative, indicating microbiological recovery. In other words, post COVID syndrome is the time lag between the microbiological recovery and clinical recovery. Majority of those with long COVID show biochemical and radiological recovery [1,2]. Long COVID can be divided into two stages- post acute COVID where symptoms extend beyond 3 weeks, but less than 12 weeks, and chronic COVID where symptoms extend beyond 12 weeks [3]. [figure 1]

Thus, among people infected with SARS-CoV-2 the presence of one or more symptoms (continuous or relapsing and remitting; new or same symptoms of acute COVID) even after the expected period of clinical recovery, irrespective of the underlying mechanism, is defined as post COVID syndrome or Long COVID. It is estimated that 31%-69% of COVID-19 survivors will experience long COVID symptoms after initial recovery from SARS-CoV-2 infection [4,5]. Generally, initial symptoms of long COVID symptoms include fatigue (29%), muscle pain, palpitations, cognitive impairment (28%), dyspnoea (21%), anxiety (27%), chest pain, and arthralgia (18%). Correspondingly, a recent meta-analysis of 36 studies identified fatigue, cognitive impairment, joint pain, anxiety, and depression as primary clinical symptoms of long COVID [6]. A massive international survey found fatigue, malaise and cognitive impairment as the most prevalence symptoms experienced among individuals with reported long COVID [7]. Approximately 30% of non-hospitalized

* Corresponding author: SHITAL PATIL; Email:Drsvpatil1980@gmail.com

COVID-19 patients reported lingering symptoms 2 months after initial infections. Similarly, less than 1% of COVID survivors achieved complete recovery at 80 days after infection [8].

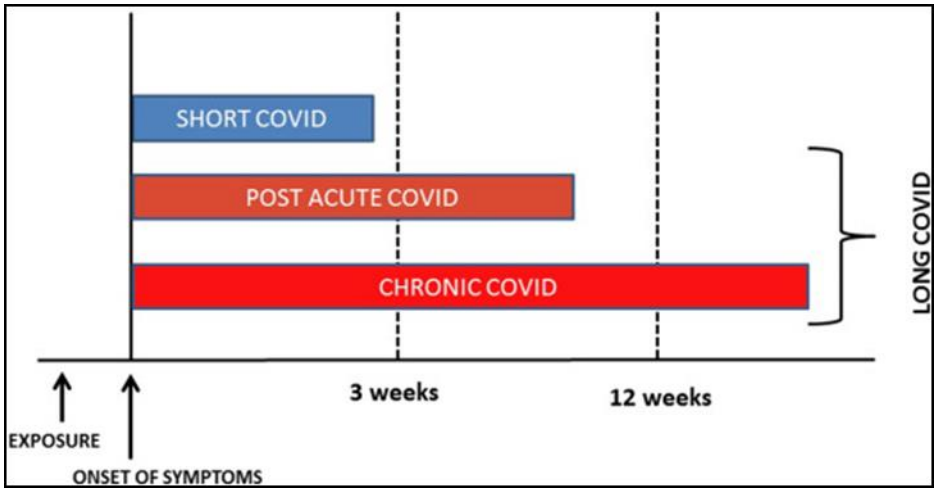

Figure 1 Classification of long COVID

The lingering symptoms of long COVID reflect chronical damages of multi-systemic organs. Such health conditions post a significant burden on the quality of life among COVID survivors [9-11]. [Figure 2] Post pandemic systemic affections and longer symptomatic phases labelled as "Long COVID" is documented in currently ongoing pandemic, and it has been also described in Russian flu, where many affected patients had crippling and long manifestations [12].

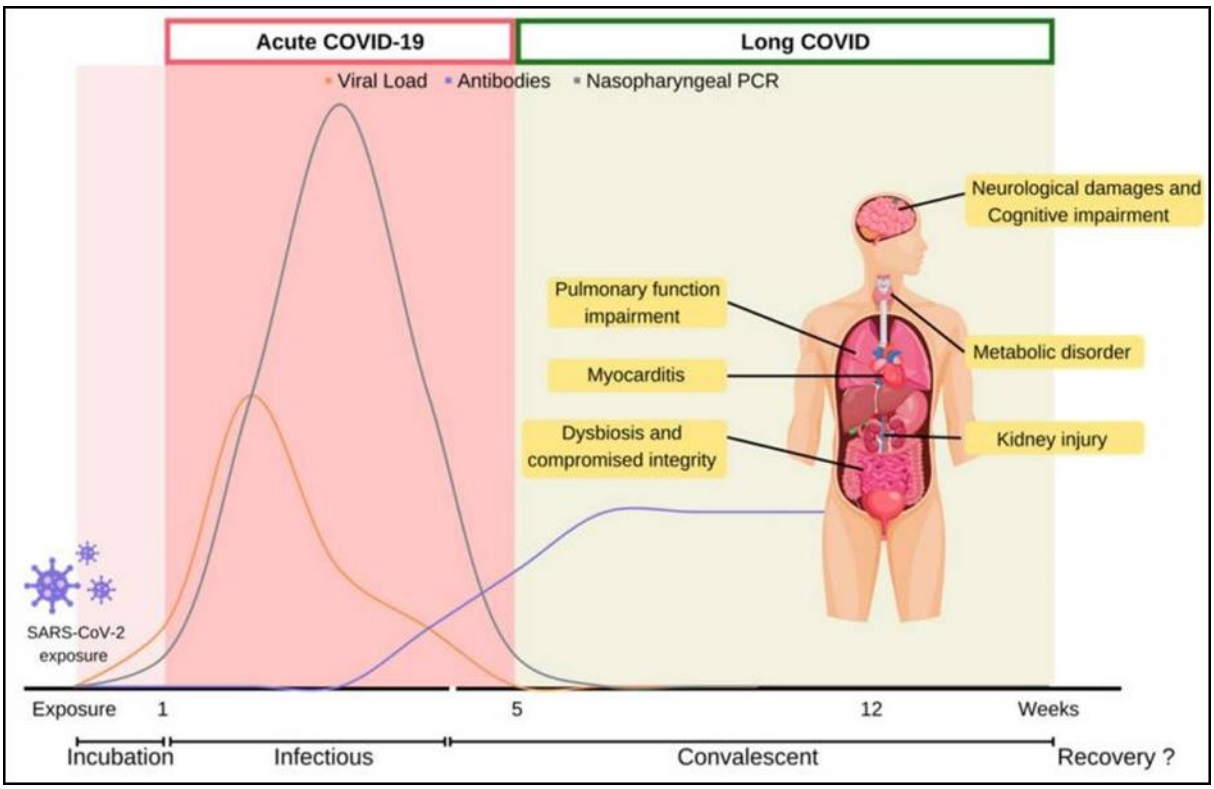

Figure 2 Disease course of COVID-19

2. Pathophysiological mechanisms for Long COVID

The exact mechanism behind the persistence of symptoms has to be identified. Reason for the persistence of symptoms can be the sequelae of organ damage, varying extent of injury (organ damage) and varying time required for the

recovery of each organ system, persistence of chronic inflammation (convalescent phase) or immune response/auto antibody generation, rare persistence of virus in the body, nonspecific effect of hospitalization, sequelae of critical illness, post-intensive care syndrome, complications related to corona infection or complications related to co morbidities or adverse effects of medications used [13,14]. [figure 3]

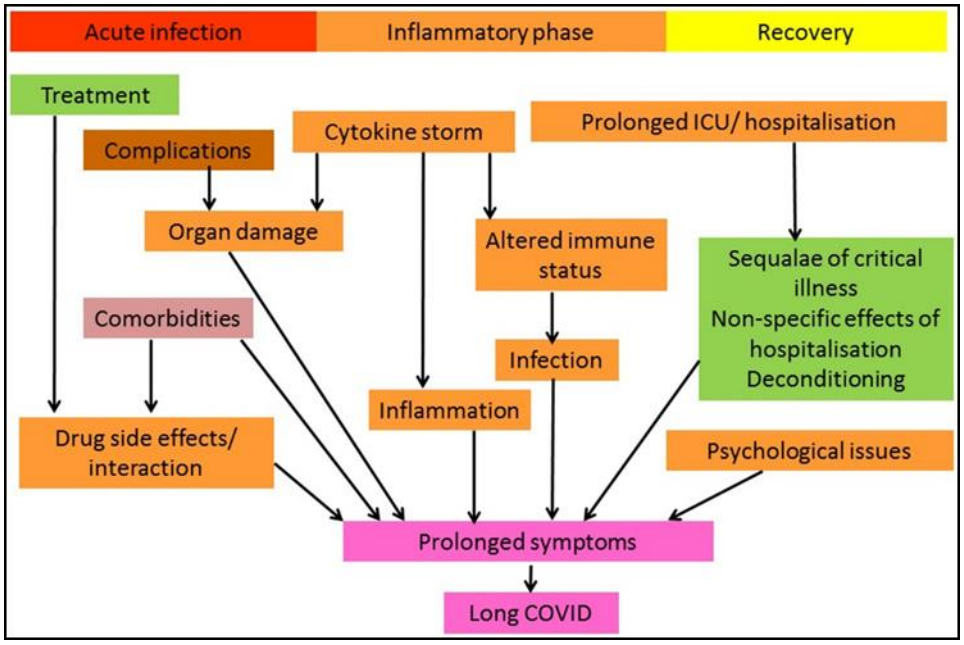

Figure 3 Various pathophysiological mechanism of "Long COVID"

2.1. Dysregulated inflammation in ongoing COVID and its impact on long COVID

COVID-19 pneumonia is heterogeneous disease with variable effect on lung parenchyma, airways and vasculature leading to long term effects on lung functions. Pathophysiological mechanism is immune activation, inflammatory, thrombogenic and direct viral affection to lungs and extrapulmonary tissues [15]. COVID-19 pandemic has been studied over last two and half years for its highly pathogenic nature of corona virus. Main hurdle for acquiring immunological memory after natural infection is genetic change in spike proteins of nucleocapsid of novel corona virus after certain interval resulting into different waves documented in different geographical settings. Dysregulation in the immune system can lead to an unappropriated local and systemic immune responses and subsequently the rapid spread of the virus, leading to severe COVID-19 disease.

Severity of illness increases with more lung parenchymal involvement as documented with chest imaging in proportion with inflammatory markers such as IL-6, CRP, Ferritin and LDH [16-19]. Authors have documented persistent smouldering infection as underlying mechanism for long COVID [20]. Second hypothesis is that mast cell activation syndrome could possibly contribute to long COVID symptomatology [21,22]. The third hypothesis put forth that sustained dysregulated immune system activation with subsequent chronic low-grade inflammation could lead to pathological consequences like autoimmunity leading to organ dysfunction [23,24]. Authors have documented long-lasting functional alterations of T-cells, with persistence of cytotoxic profile with decrease in dendritic cells revealed 7 months post-infection [25,26].

Residual excessive inflammation after infection & auto-antibodies against immunomodulatory proteins or against tissues are other proposed mechanism for long COVID [27,28]. Other possible hypothesis is persistence of SARS-CoV-2 in the lower gastro-intestinal tract was revealed in asymptomatic subjects several months after COVID-19, suggesting that residual viral proteins within tissues could possibly be the basis for a persisting immune reaction [29].

2.2. Coagulation abnormalities in ongoing COVID and its impact on long COVID

Acute COVID-19 infection is also characterized by dysregulated, circulating inflammatory biomarkers, hyperactivated platelets, damaged erythrocytes and substantial deposition of microclots in the lungs [30-32]. In those discharged with elevated biomarkers, 30.1% and 9.5% had persistently elevated D-dimer and C reactive protein, respectively. 38% of chest radiographs remained abnormal with 9% deteriorating [33]. In the largest global study to-date on this issue, a

survey of 3,762 Long COVID/PASC patients, from 56 countries found nearly half still could not work full-time 6 months post-infection, due mainly to fatigue, post-exertional malaise, and cognitive dysfunction [34].

Data is available regarding vascular changes and thrombotic microangiopathy, diffuse intravascular coagulation and large-vessel thrombosis are major reasons for a poor COVID-19 prognosis [35]. These comorbidities are linked to multisystem organ failure, as well as pulmonary vascular endothelialitis. The presence of endotheliopathy in particular, is likely to be associated with critical illness and death [36]. It is also suggested that endothelial dysfunction contributes to COVID-19-associated vascular inflammation, COVID-19-associated coagulopathy, and pulmonary fibrinous microthrombi in the alveolar capillaries. In some instances, patients present with a significant elevation in D-dimer/fibrinogen degradation products. D-dimer and fibrinogen degradation products may indicate the failing attempt of the fibrinolytic system to remove fibrin and necrotic tissue from the lung parenchyma (and also from the circulation), but being consumed or overwhelmed in the inflammatory process [37,38].

Other possible mechanism is dysregulation of the balance in fibrin-forming and fibrin-dissolving (plasmin generation) pathways and simultaneous presence of persistent anomalous (amyloid) microclots and a pathological fibrinolytic system is a major aspect of COVID-19 pathogenesis. The plasmin and antiplasmin balance may be central to this phenomenon. An important element of the fibrinolytic system is the conversion of circulating zymogen plasminogen to its active form plasmin. Endogenous activators of plasminogen are the tissue-type plasminogen activator (tPA) and urokinase-type plasminogen activator (uPA). The catalytic activity of tPA is largely dependent on the presence of fibrin, as both tPA and its substrate plasminogen bind to the lysine residues on fibrin, using it as a cofactor for plasmin generation. Plasmin is the effector protease of the fibrinolytic system, well known for its involvement in fibrin degradation and clot removal. Plasmin is also recognized as a potent modulator of immunological processes by directly interacting with various cell types including cells of the vasculature (endothelial cells, smooth muscle cells) In fact, the removal of misfolded proteins and the maintenance of tissue homeostasis seem to be major physiological functions of plasmin resulting into acute or lingering overload of anomalous (amyloid) fibrinogen microclots in circulation [39-41].

2.3. Outcomes of long COVID, interventions required for prevention and treatment of long COVID

All COVID-19 discharged symptomatic cases attending post COVID care unit needs prompt workup including vital parameters assessment and thorough systemic examination with laboratory workup and protocolised analysis [42]. [Fig 4]

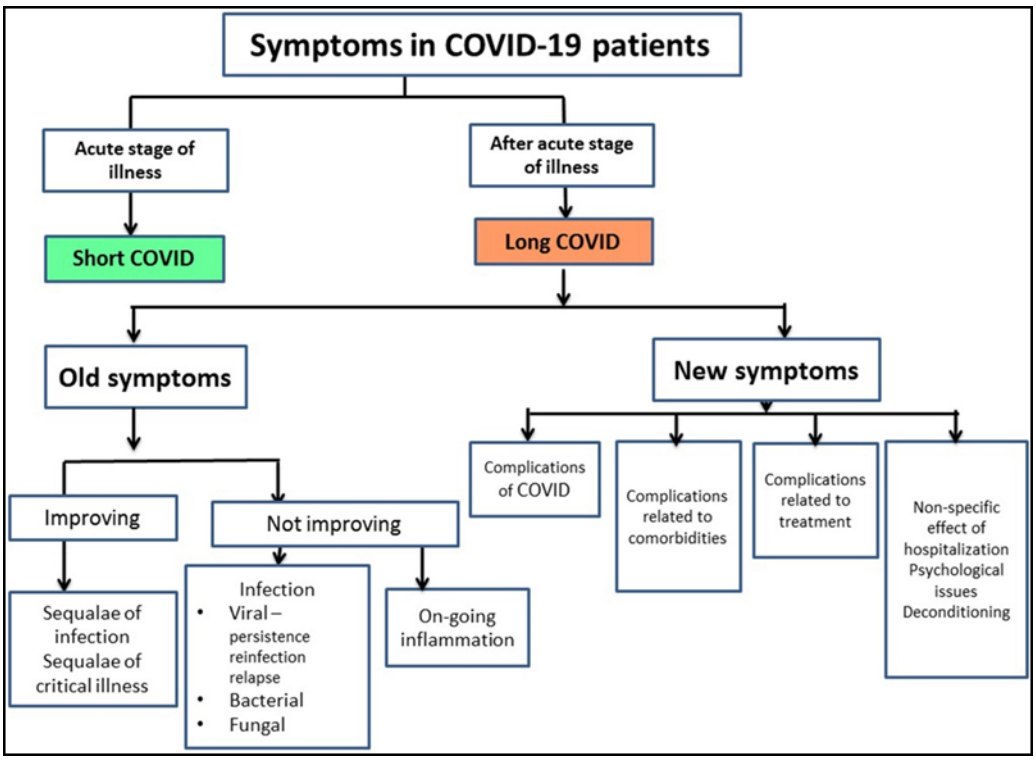

Figure 4 Approach to patients with Long COVID

2.3.1. Reversible nature of Post COVID lung fibrosis

Initially after first wave of COVID-19 pandemic, many COVID survivors in intensive care units those required oxygen supplementation, ventilatory support or high flow nasal canula, longer hospital stay, high CT severity were documented post COVID lung fibrosis. The development of pulmonary fibrosis is considered one of the key concerns regarding COVID-19 pulmonary sequelae as it is associated with architectural distortion of the lung parenchyma and overall impairment of lung function resulting in decreased quality of life. [43] The pathogenic progression of pulmonary fibrosis post-COVID-19 is yet to be fully illuminated; however, it is thought to be multifactorial. Whatever the cause, fibrosis is considered to be due to the abnormal healing of the injured lung parenchyma. In COVID-19 patients, possible sources of injury include cytokine storm due to improper inflammatory response, bacterial co-infections, and thromboembolic events causing microvascular damage and endothelial dysfunction [43]. According to the literature, pulmonary fibrosis can develop right after discharge or several weeks later [44].

Post COVID lung fibrosis at any stage ranging from minimal lung parenchymal abnormalities as parenchymal bands to reticular opacities and complete architectural distortion with or without tractional bronchiectasis and honeycombing shown near complete resolution in one to two years. Authors have also mentioned role of anti fibrotics in some cases and some cases were treated with short course of steroids. Authors have mentioned that some cases shown complete recovery without treatment with steroids and antifibrotics. Thus, post COVID lung abnormalities or lung fibrosis is completely reversible process [43].

2.3.2. Preventive measure and Treatment options for long COVID:

Medical experts are using their best efforts to manage patients with long COVID. Long COVID symptoms are presented heterogeneously, so patients need to be closely monitored. In order to develop effective treatment strategies, holistic assessment is necessary to consider pre-existing conditions and to identify specific symptoms. In long COVID, chronic inflammation provokes multi-organ damage and exacerbates pre-existing conditions. Dietary supplements, such as vitamins and minerals, contain anti-inflammatory and anti-oxidative components, so they have become potential treatments for long COVID. A pilot study demonstrates that multivitamin supplements improve clinical symptoms among long COVID patients. Nicotinamide ribose, a form of vitamin B3, is being examined for its effects of ameliorating cognitive dysfunctions and chronic fatigue. Despite the association between vitamin D deficiency and SARS-CoV-2 infection, evidence to support vitamin D supplementation for long COVID management is still lacking. Although recent study did not find an association between vitamin D levels and persistent long COVID symptoms, vitamin D deficiency is known to be associated with fatigue and muscle weakness. Additional research is warranted to explore the relationship between vitamin D and the pathology of long COVID [45].

Dietary supplements may also have beneficial effect in modulating systemic inflammation and immunity. The influence of microbiota on immunity is well known, and long COVID leads to significant changes in gut flora. Viral infection often compromises the immune system, which may increase the risk for opportunistic infections. Antibiotic and anti-viral compounds such as Azithromycin, Remdesivir and Favipiravir are being explored for their effectiveness in controlling long COVID [46]. Dexamethasone is commonly used to treat inflammation in acute COVID-19 patients. Dexamethasone-treated COVID-19 patients were less likely to experience long COVID symptoms at 8-month follow-up in an observational study [47].

Although vaccines do not prevent infection, they significantly suppress morbidity and fatality. Two recent studies compared the long COVID symptoms between unvaccinated patients and vaccinated patients. Both demonstrated that vaccination is strongly associated with the decrease of long COVID related symptoms [48,49].

3. Conclusion

Long COVID in known complication of COVID-19 disease irrespective of severity and hospitalization. Long COVID can be predicted during hospital discharge in selected cases with inflammatory and coagulation pattern abnormalities. Long COVID should be actively evaluated in those cases with aggressive interventions in indoor units and comorbidities. Importantly long COVID pulmonary manifestation as lung fibrosis is reversible and now considered as post COVID sequelae.

Long COVID is underestimated, improperly evaluated and half-heartedly treated during follow-up due to lack of suspicion especially in geriatric cases. All treated cases need prompt evaluation, more awareness regarding its manifestations and its impact on quality of life is must to have successful treatment outcome. Vaccination will prevent long COVID in majority and decrease severity of illness in survivors.

Compliance with ethical standards

Acknowledgments

Venkatesh Hospital and critical care center Latur India.

References

[1] P. Garg, U. Arora, A. Kumar, N. Wig The "post-COVID" syndrome: how deep is the damage? J Med Virol (2020 Aug), 10.1002/jmv.26465

[2] Nabavi Nikki Long COVID: how to define it and how to manage it BMJ, 370 (2020), 10.1136/bmj.m3489 m3489

[3] Trisha Greenhalgh, Matthew Knight, Christine A'Court, Maria Buxton, Laiba Husain Management of post-acute COVID-19 in primary care BMJ, 370 (2020), 10.1136/bmj.m3026 m3026

[4] Su Y, Yuan D, Chen DG, Ng RH, Wang K, Choi J. et al. Multiple early factors anticipate post-acute COVID-19 sequelae. Cell. 2022, 185:881–95.e20.

[5] Patil S, Patil R, Gondhali G. Long COVID In Post-COVID-19 Care Setting: Prospective, Observational, And Interventional Study Of 6,000 Cases In Tertiary Care Setting In India. Chest. 2022 Jun, 161(6):A538.

[6] Chen C, Haupert SR, Zimmermann L, Shi X, Fritsche LG, Mukherjee B. Global Prevalence of Post-Acute Sequelae of COVID-19 (PASC) or Long COVID: A Meta-Analysis and Systematic Review. medRxiv. 2021. 2021. 11.15.21266377.

[7] Davis HE, Assaf GS, McCorkell L, Wei H, Low RJ, Re'em Y, Characterizing long COVID in an international cohort: 7 months of symptoms and their impact. eClinicalMedicine. 2021. 38.

[8] Goërtz YMJ, Van Herck M, Delbressine JM, Vaes AW, Meys R, Machado FVC. et al. Persistent symptoms 3 months after a SARS-CoV-2 infection: the post-COVID-19 syndrome? ERJ Open Res. 2020, 6:00542–2020.

[9] Szekanecz Z, Valyi-Nagy I. Post-acute COVID-19 syndrome. Orv Hetil. 2021, 162:1067–78.

[10] Al-Aly Z, Xie Y, Bowe B. High-dimensional characterization of post-acute sequelae of COVID-19. Nature. 2021, 594:259–64.

[11] Zarei M, Bose D, Nouri-Vaskeh M, Tajiknia V, Zand R, Ghasemi M. Long-term side effects and lingering symptoms post COVID-19 recovery. Rev Med Virol. 2021: e2289.

[12] Patil S, Acharya A, Gondhali G. Does Current COVID-19 is first coronavirus-related global pandemic or history traced to 19th century as an unidentified COVID 1.0 disease "Russian Flu" apart from severe acute respiratory syndrome and Middle East respiratory syndrome?. J Appl Sci Clin Pract 2022, 3:35-8

[13] Colafrancesco, C. Alessandri, F. Conti, R. Priori COVID-19 gone bad: a new character in the spectrum of the hyperferritinemic syndrome? Autoimmun Rev, 19 (2020), 10.1016/j.autrev.2020.102573.pmid:32387470

[14] M.Z. Tay, C.M. Poh, L. Rénia, P.A. MacAry, L.F.P. Ng The trinity of COVID-19: immunity, inflammation and intervention Nat Rev Immunol, 20 (2020), pp. 363-374

[15] Patil Shital & Gajanan Gondhali (2022). Does Genetic Makeup of Corona Virus in COVID-19 Disease is as Predicted or is Similar to Other Respiratory Viruses Like Influenza? Still, we Believe in COVID Appropriate Behavior in Spite of Vaccination.Show Must Go On!. Saudi J Med, 7(1): 1-3.

[16] Patil S, Narwade G, Dhumal U. The Role of initial and follow-up C-reactive protein titer in COVID-19 pneumonia: A single-center study of 1000 cases in a tertiary care setting in India. J Adv Lung Health 2023, 3:17-24

[17] Patil S, Gondhali G, Acharya A. Role of Ferritin as "Core Marker" in the Assessment of Severity, Response to Therapy and Predicting Outcome in COVID-19 Pneumonia: A Large, Two-Center, Prospective, Observational Study of 1000 Cases in Tertiary Care Setting in India. Indian J Respir Care 2022, 11 (3):253-260.

[18] Patil S, Bhadake M, Narwade G, Patil R. Correlation of LDH with duration of illness, disease severity, ventilatory support and lung fibrosis in COVID-19 pneumonia: a single center experience of 1000 cases in tertiary care setting in India. Ital J Emerg Med 2022, 11:95-103.

[19] Patil S, Acharya A, Gondhali G, Narwade G. Serial interleukin-6 titer monitoring in COVID-19 pneumonia: Valuable inflammatory marker in the assessment of severity, predicting ventilatory support requirement, and final

radiological outcome – Prospective observational study in tertiary care setting in India. J Assoc Pulmonologist Tamilnadu 2022, 5:2-8

[20] Jacobs JJL. Persistent SARS-2 infections contribute to long COVID-19. Med Hypotheses. 2021, 149:110538.

[21] Afrin LB, Weinstock LB, Molderings GJ. COVID-19 hyperinflammation and post-COVID-19 illness may be rooted in mast cell activation syndrome. Int J Infect Dis. 2020, 100:327–332

[22] Kazama I. Stabilizing mast cells by commonly used drugs: a novel therapeutic target to relieve post-COVID syndrome? Drug Discov Ther. 2020, 14(5):259–261.

[23] Yong SJ. Long COVID or post-COVID-19 syndrome: putative pathophysiology, risk factors, and treatments. Infect Dis. 2021, 53(10):737–754.

[24] Galeotti C, Bayry J. Autoimmune and inflammatory diseases following COVID-19. Nat Rev Rheumatol. 2020, 16(8):413–414.

[25] Shuwa HA, Shaw TN, Knight SB, et al. Alterations in T and B cell function persist in convalescent COVID-19 patients. Medicine. 2021, 2(6):720–735.e4.

[26] Perez-Gomez A, Vitalle J, Gasca-Capote C, et al. Dendritic cell deficiencies persist seven months after SARS-CoV-2 infection. Cell Mol Immunol. 2021, 18(9):2128–2139.

[27] Doykov I, Hallqvist J, Gilmour KC, et al. The long tail of COVID-19' – the detection of a prolonged inflammatory response after a SARS-CoV-2 infection in asymptomatic and mildly affected patients. F1000Res. 2020, 9:1349.

[28] Wang EY, Mao T, Klein J, et al. Diverse functional autoantibodies in patients with COVID-19. Nature. 2021, 595(7866):283–288.

[29] Gaebler C, Wang Z, Lorenzi JCC, et al. Evolution of antibody immunity to SARS-CoV-2. Nature. 2021, 591(7851):639–644.

[30] Venter C, Bezuidenhout JA, Laubscher GJ, Lourens PJ, Steenkamp J, Kell DB, Pretorius E. Erythrocyte, platelet, serum ferritin, and P-selectin pathophysiology implicated in severe hypercoagulation and vascular complications in COVID-19. *Int J Mol Sci.* 2020, **21**(21):8234.

[31] Patil S, Acharya A, Gondhali G, Narwade G. Role of 'Serial D-Dimer Level' in predicting Severity and outcome in COVID-19 pneumonia: A Prospective multicentric Observational Study of 1000 cases in Tertiary Care Setting in India. EJMA 2022, 2(2):73–80.

[32] Bobrova L, Kozlovskaya N, Korotchaeva Y, Bobkova I, Kamyshova E, Moiseev S. Microvascular COVID-19 lung vessels obstructive thromboinflammatory syndrome (MicroCLOTS): a new variant of thrombotic microangiopathy? Crit Care Resusc. 2020, 22(3):284.

[33] Mandal S, Barnett J, Brill SE, Brown JS, Denneny EK, Hare SS, Heightman M, Hillman TE, Jacob J, Jarvis HC, et al. 'Long-COVID': a cross-sectional study of persisting symptoms, biomarker and imaging abnormalities following hospitalisation for COVID-19. Thorax. 2020, 76:396–398.

[34] Komaroff AL, Bateman L. Will COVID-19 lead to myalgic encephalomyelitis/chronic fatigue syndrome? Front Med (Lausanne) 2020, 7:606824.

[35] Ackermann M, Verleden SE, Kuehnel M, Haverich A, Welte T, Laenger F, Vanstapel A, Werlein C, Stark H, Tzankov A, et al. Pulmonary vascular endothelialitis, thrombosis, and angiogenesis in COVID-19. N Engl J Med. 2020, 383(2):120–128.

[36] Goshua G, Pine AB, Meizlish ML, Chang CH, Zhang H, Bahel P, Baluha A, Bar N, Bona RD, Burns AJ, et al. Endotheliopathy in COVID-19-associated coagulopathy: evidence from a single-centre, cross-sectional study. Lancet Haematol. 2020, 7(8):e575–e582.

[37] Wool GD, Miller JL. The impact of COVID-19 disease on platelets and coagulation. Pathobiology. 2021, 88(1):15–27.

[38] Medcalf RL, Keragala CB, Myles PS. Fibrinolysis and COVID-19: a plasmin paradox. J Thromb Haemost. 2020, 18(9):2118–2122.

[39] Draxler DF, Sashindranath M, Medcalf RL. Plasmin: a modulator of immune function. Semin Thromb Hemost. 2017, 43(2):143–153.

[40] Cesarman-Maus G, Hajjar KA. Molecular mechanisms of fibrinolysis. Br J Haematol. 2005, 129(3):307–321.

[41] Kwaan HC, Lindholm PF. The central role of fibrinolytic response in COVID-19-a hematologist's perspective. Int J Mol Sci. 2021, 22(3):1283.

[42] Raveendran AV, Jayadevan R, Sashidharan S. Long COVID: An overview. Diabetes Metab Syndr. 2021 May-Jun, 15(3):869-875. doi: 10.1016/j.dsx.2021.04.007. Epub 2021 Apr 20. Erratum in: Diabetes Metab Syndr. 2022 May, 16(5):102504.

[43] Shital Vishnu Patil, Gajanan Gondhali, Rajesh Patil Post-COVID-19 Lung Fibrosis: Study of 600 cases in tertiary care setting in India. European Respiratory Journal 2021 58: PA3776, DOI: 10.1183/13993003.congress-2021.PA3776

[44] Fernandez I.E., Eickelberg O. New cellular and molecular mechanisms of lung injury and fibrosis in idiopathic pulmonary fibrosis. Lancet. 2012, 380(9842):680–688.

[45] Naureen Z, Dautaj A, Nodari S, Fioretti F, Dhuli K, Anpilogov K. et al. Proposal of a food supplement for the management of post-COVID syndrome. Eur Rev Med Pharmacol Sci. 2021, 25:67–73

[46] Koc HC, Xiao J, Liu W, Li Y, Chen G. Long COVID and its Management. Int J Biol Sci. 2022 Jul 11, 18(12):4768-4780

[47] Milne A, Maskell S, Sharp C, Hamilton F, Arnold D. Impact of dexamethasone on persistent symptoms of COVID-19: an observational study. medRxiv. 2021. 2021. 11.17.21266392

[48] Kuodi P, Gorelik Y, Zayyad H, Wertheim O, Wiegler KB, Jabal KA, Association between vaccination status and reported incidence of post-acute COVID-19 symptoms in Israel: a cross-sectional study of patients tested between March 2020 and November 2021. medRxiv. 2022. 2022. 01.05.22268800.

[49] Antonelli M, Penfold RS, Merino J, Sudre CH, Molteni E, Berry S. et al. Risk factors and disease profile of post-vaccination SARS-CoV-2 infection in UK users of the COVID Symptom Study app: a prospective, community-based, nested, case-control study. The Lancet Infectious Diseases. 2022, 22:43–55