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Review Article

Hydroxychloroquine as 'Potential Treatment Option' for Persistent Immune Dysregulation in Long COVID: Revisiting Its New Use as a 'Versatile' Molecule!

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Abstract: COVID-19 pandemic is over now and we are in great peace of relief after three years of first case reported in China. This pandemic has observed a significant impact on quality of life globally and this puts unforgettable imprints on the history of mankind. Reason for more havoc in this pandemic was less studied virus before this 'unpredicted or surprise pandemic' by medical scientists regarding its pathophysiology, available treatment options and lack of effective vaccine to tackle this dragon. Rationale would be COVID-19 is the first observed and reported pandemic of corona virus related global disease apart from its previously occurring SARS and MERS Epidemics. Fast track developments in medical treatment options with use of ultrafast digital and artificial intelligence techniques have curtailed mortality on a large scale globally. Although mortality is significantly reduced, morbidity is documented in significant number of cases worldwide after this Dragon related pandemic. Morbidity due to COVID-19 now called as 'Long COVID', which is underreported & half-heartedly evaluated globally. Long COVID is related to persistent immune dysregulation which occurred during evolution of COVID-19 as a natural trend of disease & documented during the course of active viremia, during recovery of viral illness and after the post viral phase. Immune dysregulation occurs in a 'selected group' of cases irrespective of disease severity and vaccination status, and observed in cases irrespective of severity of illness as with negligible illness resulted into brainstorming effect on medical scientists and researchers as of today to advanced and mandates further global research. Globally, one third of recovered or affected cases of COVID-19 are facing long covid and need prompt treatment options to tackle this dragon related long term effect on body. 'Immunomodulatory' or immunity modifying agents are the primary targets to curtail immune dysregulation and long covid. Some experts recommend 'disease modifying agents' to treat long covid cases. Still, many miles to go to reach effective treatment options for long covid and we don't have effective options as of now for this 'health issue of global concern' related to Dragon. Hydroxychloroquine is initially used as an antimalarial and as an anti-inflammatory molecule for decades in various rheumatic conditions with satisfactory results. Despite decades of dependable use and predictable results in the treatment of rheumatic disease, HCQ remains a drug with an ever-expanding number of underlying mechanisms. HCQ was tried initially for prophylaxis treatment of COVID-19 due to its anti-inflammatory properties but has not shown any dramatic results. WHO has removed HCQ from the treatment plan after many trial results with disappointing outcomes. HCQ is a drug with multiple beneficial pleiotropic effects such as immunomodulatory effects which regulates immunological responses that inhibit dysregulated immune system. These Immunomodulatory and or diseases modifying effects of HCQ makes it the future candidate with 'game changer' role for management of Long covid resulting from immune dysregulation as a core pathophysiologic pathway of this Dragon Pandemic. Revisiting this old drug with 'versatile effects' can be used as treatment option for short time as frontline molecule for Long covid when no definitive options are available after consideration of risk benefit ratio which is a cost-effective treatment option.

Keywords: Immune dysregulation, COVID-19, Long COVID, Hydroxychloroquine, Immunomodulatory.

Inflammatory response and inflammatory markers in COVID-19 pneumonia

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. The immune response during acute illness contributes to both host defence and pathogenesis of severe COVID-19 [1-2]. Now the robust data is available for role of various inflammatory markers in initial assessment of cases which are associated with direct or indirect virus-related lung injury. This is first COVID-19 related global pandemic in history of mankind and more studied pandemic in all waves in all viral pandemics due to its rapid evolution and high mortality [3-5]. Apart from lung involvement, proportionate number of cases were shown systemic manifestations due to activation of inflammatory pathway and inflammatory surge resulting in to pulmonary and extrapulmonary effects which have significant impact on final outcome. All these effects can be easily picked up by timely analysis of inflammatory markers. Now these markers are also called as 'inflammatory biomarkers.' Various inflammatory markers such as CRP, Ferritin, LDH, D-dimer and IL-6 were exuberantly used during workup of COVID-19 cases worldwide and reported their valuable role in initial assessment, predicting severity, guiding or triaging hospitalization, predicting need of interventions during hospitalization, analysing final outcome, predicting post recovery outcome and possibility of long covid manifestations and considered as 'composite index' [6-7]. Various treatment options used in COVID-19 pneumonia have showed significant impact on inflammatory markers during course of hospitalization [7-8]. Inflammatory markers has been studied for predicting antigenic cross-reactivity and antigenic mimicry which has resulted in autoimmune and rheumatological manifestations. During COVID-19 pandemic antigenic cross reactivity has documented with dengue fever [10-13]. Similarly, deregulated immune phenomenon has been documented after covid vaccination and transient autoimmune features have been reported in various studies [14-15]. COVID-19 related extrapulmonary manifestations have been reported secondary to dysregulated immune response and systemic effects on immunity & immunosuppression resulting into tuberculosis [16], central nervous system resulting into stroke [17] and endocrinal effects resulting into hyponatremia [18]. Disease outcomes range from asymptomatic and mild to more severe and critical courses with pneumonia, acute respiratory distress syndrome (ARDS), multiorgan failure, and considerable risk of fatality. In this context, the immune cell landscape of severe COVID-19 patients is reported to be dysregulated and detailed insights on the cellular dynamics of severe COVID-19 patients are urgently needed to identify potential disease intervention points [19]. Previous studies have shown dysregulation of innate and adaptive immune cell compartments in patients with moderate, severe, and convalescent COVID-19 [19]. 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, LDH and D-dimer [20-39].

Basic Pathophysiology of Immune dysregulation during evolution of COVID-19:

Coronaviruses (CoVs) are the largest group of viruses belonging to the Nidovirales order and Coronaviridae family. Coronaviridae is further divided into two subfamilies, Coronavirinae and Torovirinae. The alpha, beta, gamma, and delta coronaviruses belong to Coronavirinae. There are seven coronaviruses that infect humans and have been identified since the mid-1960s. They consist of 1) 229E (alpha coronavirus), 2) NL63 (alpha coronavirus), 3) OC43 (beta coronavirus), 4) HKU1 (beta coronavirus), 5) MERS-CoV (the beta coronavirus), 6) SARS-CoV (the beta coronavirus) and 7) SARS-CoV2 (the beta coronavirus COVID-19) [40] The virus initially binds to the host cell's receptor via the S protein, and more specifically, the S1 domain/subunit of S protein. Depending on the type of coronavirus, the receptor-binding domains (RBD) within the S1 subunit/region can vary [41]. The S-protein–receptor interaction governs the tissue tropism of the virus.

Table 1: Types of Corona virus and their host receptors [42]

Coronaviriniae Genera	Strain	Receptor	host
Alpha-coronavirus	HCoV-229E	Human Aminopeptidase N (CD13)	Bats
	HCoV-NL63	ACE2	Palm Civets, Bats
Beta-coronavirus	HCoV-OC43	9-O-Acetylated sialic acid	Cattle
	HcoV-HKU1	9-O-Acetylated sialic acid	Mice
	SARS-CoV1	ACE2	Palm Civets, Bats
	MERS-CoV	DPP4	Bats, Camels
	SARS-CoV2	ACE2	Bats

For example, angiotensin-converting enzyme 2 (ACE2) serves as the receptor for the SARS-CoV and HCoV-NL63, whereas dipeptidyl-peptidase 4 serves as the receptor for MERS-CoV. Subsequently, the virus enters the cytosol by acid-dependent proteolytic cleavage of the S protein, primarily by the protease cathepsin, though other proteases can play this role. Finally, fusion of the viral and host cellular membranes occur in the acidified endosome of the host cell, ultimately releasing the viral genome into the cytoplasm. Following

replication and assembly, virions are transported to the cell surface through vesicles and released by exocytosis [43]. Upon viral infection with the SARS-CoV, the antigen presenting cells (APC) process the viral antigen and present the processed antigen to the T-cells by MHC class 1 [44]. Antigen presentation activates humoral and cellular immunity responses by B and T cells, respectively. The antibody profiles against the SARS-CoV2 virus have a typical pattern of IgM and IgG production. Predominantly, S and N specific antibodies are produced. The SARS-specific IgM antibodies disappear at the end of week 12, whereas the IgG antibodies can last for a long time, suggesting that the IgG antibodies may have a protective role [45].

Role of Hydroxychloroquine as an antiviral and immune modulatory during acute COVID-19

Throughout history, the antimalarial HCQ and its predecessors quinine, quinacrine, and chloroquine (CQ) have proven to be therapeutically versatile. The synthesis of HCQ in 1946 by American chemists Alexander Surrey and Henry Hammer provided a conveniently produced, economical, safe, and better tolerated medication than its immediate parent drug CQ. First approved for use in 1955, HCQ is currently approved by the US Food and Drug Administration to treat malaria, discoid and systemic lupus erythematosus, and rheumatoid arthritis. However, numerous off-label uses exist including cutaneous dermatomyositis, extra-glandular manifestations of Sjogren's syndrome, sarcoidosis, antiphospholipid syndrome, porphyria cutanea tarda, and Q fever. The far-reaching therapeutic range of HCQ is partially due to its unique and highly variable pharmacokinetic profile as well as its multiple proposed mechanisms of action [46]. Several potential antiviral mechanisms for HCQ have been proposed, including interfering with viral surface receptor binding, biosynthesis of sialic acids and subsequent ligand recognition, pH gradient-dependent endosome-mediated cell entry and virus-endosome fusion, viral uncoating, posttranslational modification of the viral protein, proteolytic processing, viral budding, and maturation of the viral protein, among others [38]. HCQ also has immunomodulatory effects that are possibly effective against viruses, including improving the transport of viral particles to dendritic presenting cells and subsequent CD8+ T cell activation, as well as inhibition of p38 mitogen-activated protein kinase (MAPK) signaling, which is important for viral replication. Further contributing to a largely anti-inflammatory response against pathogens, CQ and HCQ are thought to inhibit TLR 7 and 9 signaling, thus reducing production of pro-inflammatory cytokines and evolution into cytokine storm [47-49].

During one of the earliest prospective cohort analyses of COVID-19 patients in February of 2020, Huang *et al.,* noted that patients infected with SARS-CoV-2 virus had a highly proinflammatory cytokine profile and that elevations in some of these cytokines, such as granulocyte colony-stimulating factor (G-CSF) and tumor necrosis factor-alpha (TNF-α), were predictive of more severe disease [50]. Shortly thereafter, Chen *et al.*, performed a retrospective review of COVID-19 patients, noting significantly higher levels of proinflammatory molecules, including interleukin-2 receptor (IL-2R) and interleukin-6 (IL-6), significantly lower CD4+ T cells and CD8+ T cells, significantly lower naïve CD45RA+ T regulatory cells, and a trend toward lower natural killer cells in severe cases as compared to moderate cases [51]. These studies highlight the ways in which hyperinflammation and immune system dysfunction contribute to the pathogenesis of COVID-19 [52]. In theory, immune-modulating therapies such as HCQ could help tip the immune response toward a less inflammatory state, curb production of proinflammatory cytokines, and prevent progression to a deadly cytokine storm.

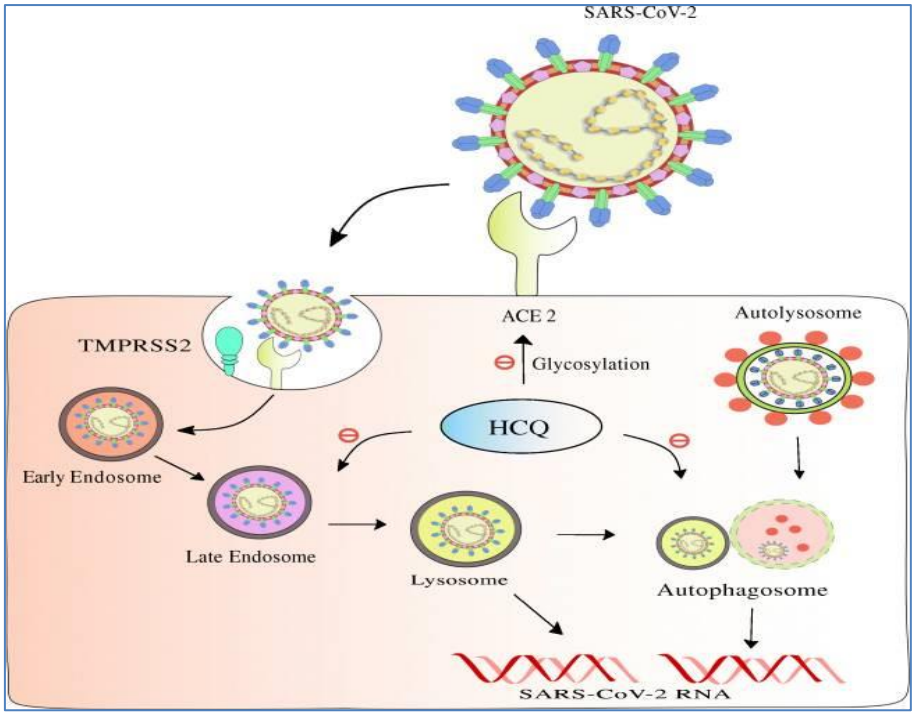

Figure 1: It is showing the role of CQ/HCQ in inhibition of ACE2 glycosylation, conversion of early endosome into late endosome and formation of autophagosome (transmembrane serine protease II (TMPRSS2) facilitate the S priming) [53]

Possible role of HCQ in preventing cytokine storm

Recently, a striking feature was observed in severely ill patients in China whose plasma profiles showed elevated levels of cytokines. Therefore, it would not be wrong to associate such an increase in levels of cytokines, termed as a cytokine storm, to grade how severe the disease is progressing. In the antigen-presenting cells (APC), HCQ inhibits the antigen processing and presentation of autoantigen mediated by the major histocompatibility complex (MHC) class II to T cells. Due to this, the levels of activated T cells decline, causing a reduction in the production of cytokines generated by T cells and the B cells. The changes in pH caused by HCQ also affects the toll-like receptor (TLR) functioning. Synergistically, HCQ can also associate with nucleic acids to block TLR9 binding and RNA facilitated activation of TLR 7 processing, therefore, reducing the production of cytokines. The cyclic GMP-AMP (cGAMP) synthase (cGAS) upon binding to DNA leads to the formation of cGAMP. This cGAMP upon associating with stimulator of interferon gene protein (STING) leads to the generation of interferon 1 (IFN I) via the interferon regulatory transcription factor (IRF) [54-55].

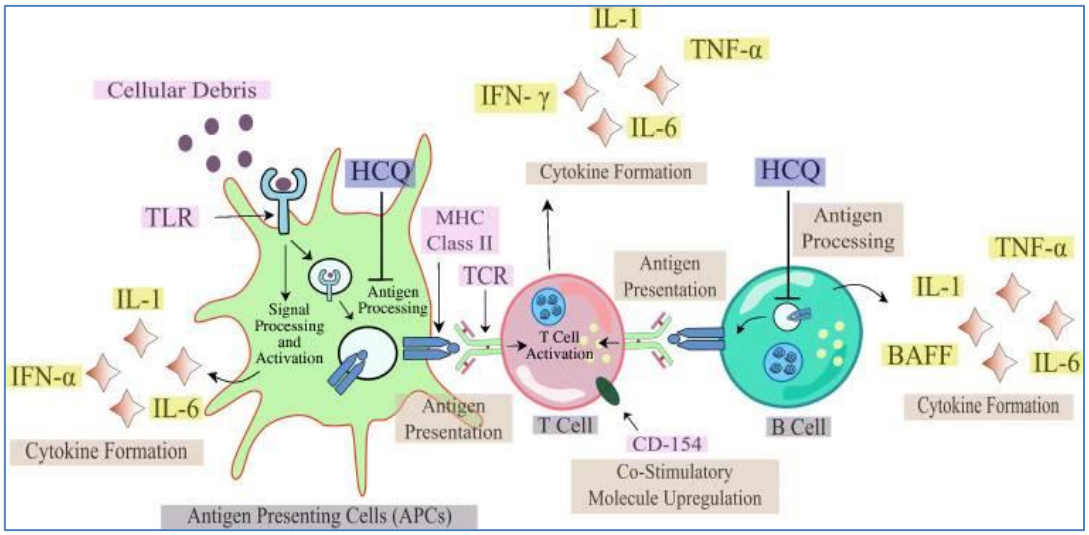

Figure 2: Showing the role of HCQ in prevention of cytokine storm via inhibition of antigen processing and TLR receptor binding in antigen-presenting cells (APCs) [53]

Limitations for wide scale use of HCQ in acute COVID-19

The first major randomized controlled trial examining HCQ in COVID-19 published in the peer-reviewed literature appeared on May 6, 2020, by Tang *et al.*, [56]. This study compared HCQ with standard of care in 150 hospitalized patients with COVID-19 across 16 medical centers in China, finding no difference in the negative conversion rate of SARS-CoV-2 by 28 days [56]. A pivotal initial study published on March 20, 2020, by Gautret *et al.*, reported on 42 patients with or without exposure to HCQ, suggesting lower viral carriage in those treated with HCQ and particularly low viral carriage in those treated with both HCQ and azithromycin. Importantly, clinical efficacy endpoints beyond nasal carriage were not discussed [57]. A randomized controlled trial in 62 patients suggesting efficacy of HCQ for COVID-19 [58] and a very recently published observational study from the US Veterans Health Administration health system that suggested an association between HCQ and increased overall mortality in hospitalized patients with COVID-19 [59]. Subsequently, multiple additional randomized-controlled trials have replicated these findings in hospitalized patients, while also demonstrating lack of efficacy for post-exposure prophylaxis or in outpatients with mild infections. Other major studies have been halted due to lack of efficacy, including the HCQ arm of the World Health Organization SOLIDARITY trial, the UK National Institute for Health Research RECOVERY trial, and the US National Institutes of Health ORCHID trial [46]. WHO does not recommend hydroxychloroquine as a treatment for COVID-19. This recommendation is based on findings from 30 trials with more than 10 000 COVID-19 patients. Hydroxychloroquine did not reduce mortality, the need for or duration of mechanical ventilation. Taking hydroxychloroquine to treat COVID-19 may increase the risk of heart rhythm problems, blood and lymph disorders, kidney injury, liver problems and failure.

Immune dysregulation as frontline mechanism of long COVID

Long COVID is an often-debilitating illness that occurs in at least 10% of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections. More than 200 symptoms have been identified with impacts on multiple organ systems. At least 65 million individuals worldwide are estimated to have long COVID, with cases increasing daily [60]. Biomedical research has made substantial progress in identifying various pathophysiological changes and risk factors and in characterizing the illness; further, similarities with other viral-onset illnesses such as myalgic encephalomyelitis/chronic fatigue syndrome and postural orthostatic tachycardia syndrome have laid the groundwork for research in the field [60-69]. There are likely multiple, potentially overlapping, causes of long COVID. Several hypotheses for its pathogenesis have been suggested, including persisting reservoirs of SARS-CoV-2 in tissues; immune dysregulation with or without reactivation of underlying pathogens, including herpesviruses such as Epstein–Barr virus (EBV) and human herpesvirus 6 (HHV-6) among others; impacts of SARS-CoV-2 on the microbiota, including the virome; autoimmunity and priming of the immune system from molecular mimicry; microvascular blood clotting with endothelial dysfunction; and dysfunctional signalling in the brainstem and/or vagus nerve [60-70].

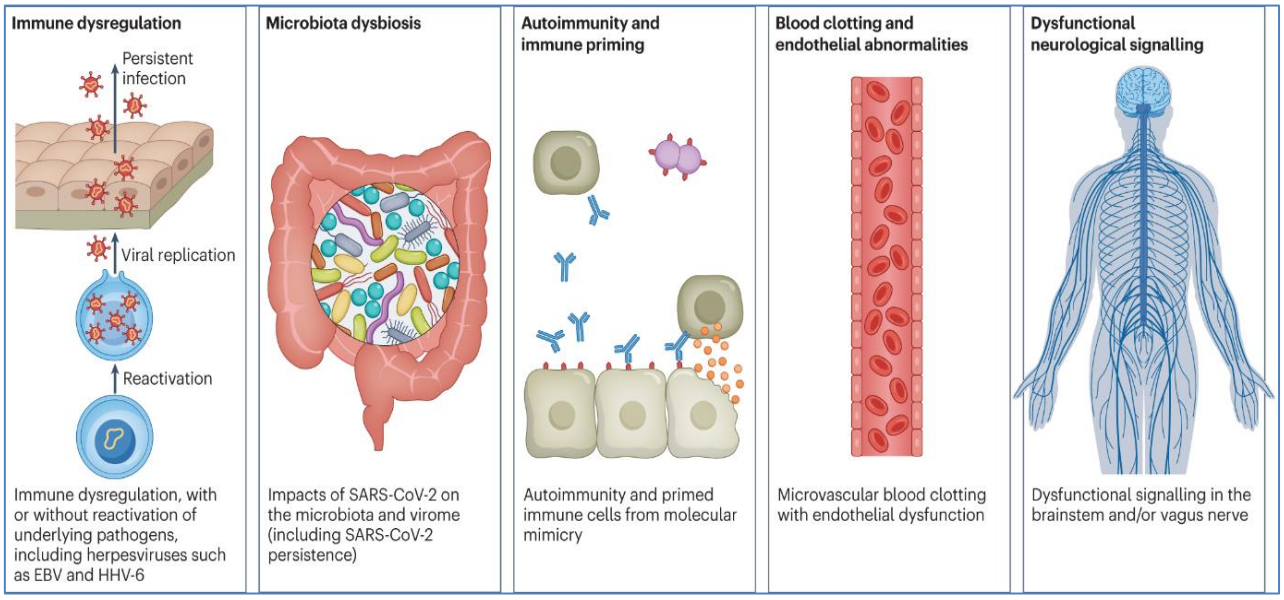

Figure 3: Hypothesized mechanisms of long COVID pathogenesis [60]

There are several hypothesized mechanisms for long COVID pathogenesis, including immune dysregulation, microbiota disruption, autoimmunity, clotting and endothelial abnormality, and dysfunctional neurological signalling. EBV, Epstein–Barr virus; HHV-

6, human herpesvirus 6; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

1. Studies looking at immune dysregulation in individuals with long COVID who had mild acute COVID-19 have found T cell alterations, including exhausted T cells, reduced CD4+ and CD8+ effector memory cell numbers and elevated PD1 expression on central memory cells, persisting for at least 13 months [71].
2. Studies have also reported highly activated innate immune cells, a lack of naive T and B cells and elevated expression of type I and type III interferons (interferon-β (IFNβ) and IFNλ1), persisting for at least 8 months [72].
3. A comprehensive study comparing patients with long COVID with uninfected individuals and infected individuals without long COVID found increases in the numbers of non-classical monocytes, activated B cells, double-negative B cells, and IL-4- and IL-6-secreting CD4+ T cells and decreases in the numbers of conventional dendritic cells and exhausted T cells and low cortisol levels in individuals with long COVID at a median of 14 months after infection [73].
4. The expansion of cytotoxic T cells has been found to be associated with the gastrointestinal presentation of long COVID. Additional studies have found elevated levels of cytokines, particularly IL-1β, IL-6, TNF and IP10, and a recent preprint has reported persistent elevation of the level of CCL11, which is associated with cognitive dysfunction. It remains to be seen whether the pattern of cytokines in myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS), where the levels of certain cytokines are elevated in the first 2–3 years of illness but decrease over time without a corresponding decrease in symptoms, is similar in long COVID [74-75].
5. Multiple studies have found elevated levels of autoantibodies in long COVID27, including autoantibodies to ACE2 (the receptor for SARS-CoV-2 entry), β2-adrenoceptor, muscarinic M2 receptor, angiotensin II AT1 receptor and the angiotensin 1–7 MAS receptor. High levels of other autoantibodies have been found in some patients with COVID-19 more generally, including autoantibodies that target the tissue (such as connective tissue, extracellular matrix components, vascular endothelium, coagulation factors and platelets), organ systems (including the lung, central nervous system, skin and gastrointestinal tract), immunomodulatory proteins (cytokines, chemokines, complement components and cell-surface proteins). A major comprehensive study, however, did not find autoantibodies to be a major component of long COVID [76-77].
6. Reactivated viruses, including EBV and HHV-6, have been found in patients with long COVID (and have been identified in ME/CFS45), and lead to mitochondrial fragmentation and severely affect energy metabolism46. A recent preprint has reported that EBV reactivation is associated with fatigue and neurocognitive dysfunction in patients with long COVID [73].
7. Several studies have shown low or no SARS-CoV-2 antibody production and other insufficient immune responses in the acute stage of COVID-19 to be predictive of long COVID at 6–7 months, in both hospitalized patients and non-hospitalized patients. These insufficient immune responses include a low baseline level of IgG, low levels of receptor-binding domain and spike-specific memory B cells, low levels of nucleocapsid IgG and low peaks of spike-specific IgG. In a recent preprint, low or absent CD4+ T cell and CD8+ T cell responses were noted in patients with severe long COVID, and a separate study found lower levels of CD8+T cells expressing CD107a and a decline in nucleocapsid-specific interferon-γ-producing CD8+T cells in patients with long COVID compared with infected controls without long COVID. High levels of autoantibodies in long COVID have been found to be inversely correlated with protective COVID-19 antibodies, suggesting that patients with high autoantibody levels may be more likely to have breakthrough infections. SARS-CoV-2 viral rebound in the gut, possibly resulting from viral persistence, has also been associated with lower levels and slower production of receptor-binding domain IgA and IgG antibodies. There are major differences in antibody creation, seroreversion and antibody titre levels across the sexes, with women being less likely to seroconvert, being more likely to serorevert and having lower antibody levels overall, even affecting antibody waning after vaccination [78-80].
8. Several reports have pointed towards possible viral persistence as a driver of long COVID symptoms; viral proteins and/or RNA has been found in the reproductive system, cardiovascular system, brain, muscles, eyes, lymph nodes, appendix, breast tissue, hepatic tissue, lung tissue, plasma, stool and urine [81-82]. In one study, circulating SARS-CoV-2 spike antigen was found in 60% of a cohort of 37 patients with long COVID up to 12 months after diagnosis compared with 0% of 26 SARS-CoV-2-infected individuals, likely implying a reservoir of active virus or components of the virus. Indeed, multiple reports following gastrointestinal biopsies have indicated the presence of virus, suggestive of a persistent reservoir in some patients [84].
9. Immune dysregulation has been documented in long covid cases especially those cases required long term hospitalization, those required ventilatory support or oxygen supplementation, those required oxygen or ventilatory support at home. These classes of patients were having post covid lung sequel as long covid manifestations [85-90]. These cases can be picked up during hospitalization by analysing CT severity and typical radiological phenotypes. Radiological phenotyping is natural

trend of evolution of COVID-19 pneumonia at entry point. Presence or absence of GGOs, consolidations and crazy paving with necrosis were key radiological markers in categorizing these phenotypes. Radiological phenotyping should be correlated with clinical and laboratory parameters for accurate analysis of severity assessment, duration illness prediction and inflammatory markers workup. Phenotyping will also help in monitoring of COVID-19 pneumonia cases and guide for necessary timely interventions in indoor units to have successful treatment outcome. Post covid fibrosis is reversible and should be labelled as sequalae due to near total reversible nature [90-93].

HCQ could be explored as a potential therapeutic agent in long COVID for a few reasons [46, 94-97]

1. Immunomodulation through inhibition of toll-like receptor (TLR) 7/9. HCQ inhibits TLR signaling by altering the pH of endosomes involved in TLR processing and/or preventing TLR7/9 from binding to their respective ligands (RNA and DNA).
2. HCQ is able to inhibit cytokine production in various immune cells, for example, the production of IL-1, IL-6, TNF, and IFNγ by mononuclear cells and the production of TNF, IFNα, and IL-6 by plasmacytoid dendritic cells and natural killer cells
3. Therefore, HCQ may dampen the unremitting hyperinflammatory response seen in long COVID by suppressing TLR 7/9 activation, pro-inflammatory cytokine release, and also subsequent immune activation.
4. Preventing MHC class II-mediated autoantigen presentation through lysosomal inhibition. HCQ might address this problem through the prevention of MHC class II-mediated autoantigen presentation through inhibition of lysosomal activity. HCQ inhibits the degradation of cargo derived externally (via endocytosis or phagocytosis) or internally (via the autophagy pathway) in autolysosomes by increasing the pH of endosomal compartments, impairing the maturation of lysosomes and autophagosomes, and inhibit auto-antigen presentation along the lysosomal pathway
5. Inhibit the cGAS–stimulator of the IFN genes (STING) pathway, which can reduce the production of pro-inflammatory cytokines. HCQ can also exert its immunomodulatory effects through the inhibition of nucleic acid sensor cyclic GMP-AMP (cGAMP) synthase (cGAS) by interfering with cGAS binding to cytosolic DNA. cGAS stimulator of IFN genes (STING) pathway is a major source of the type I interferon (IFN) response, and through inhibition of this pathway, it can reduce the production of pro-inflammatory cytokines, including type I IFN.
6. HCQ is well-proven to reduce thromboembolic events in auto-immune conditions like SLE. Immunomodulatory effects of HCQ may result in less immune-mediated microthromboses. Another postulated mechanism of long COVID is a sustained endotheliopathy due to microthrombi; it was noted that in patients with long COVID, their plasma vWF antigen and propeptide levels correlated inversely with exercise capacity. HCQ is well-proven to reduce thromboembolic events in SLE and improve endothelial dysfunction. Assuming that the ongoing endotheliopathy is associated with immune-mediated microthromboses, HCQ could potentially improve endothelial dysfunction that is also found in the pathogenesis of long COVID.
7. Chronic autoimmune hyperinflammatory process.
8. Sustained endotheliopathy secondary to microthrombi.

CONCLUSIONS

Immune dysregulation is documented during evolution of COVID-19 illness and observed in post covid care settings in those facing long covid manifestations. Robust data is available regarding the potential role of immune dysregulation in long covid pathophysiology. As of today, we don't have an answer to management of Immune dysregulation in the long covid. Definite treatment options for long covid are still underway and many experimental drugs have shown some benefit in small studies. Researchers have documented some relief of Immune dysregulation and long covid after vaccination, but we are not sure whether vaccination or patients own immune switch between TH1 and Th2 has played a role restoring immunity. Vaccination has resulted in immune dysregulation related rheumatological and autoimmune manifestations, hence the full proof protective role of the vaccine in restoring immunity after natural COVID-19 related immune dysregulation is the real question. Even after three years of COVID-19 pandemic, we have no effective treatment for long covid. Initially we thought a great breath of relief as this pandemic has weaned off but real danger is immune dysregulation which is persisting even after complete clinical recovery irrespective of severity and hospitalization. Effect of treatment options used during ongoing COVID-19 illness during hospitalization have not shown any benefit in curtailing immune dysregulation in post covid care settings. Immune dysregulation has been documented irrespective of use of medicines during evolution of illness in outdoor or indoor setting and irrespective of use of the medicines which has shown benefit in curtailing inflammatory surge or burst during the course of natural disease. Thus, immune dysregulation is not related to the outcome of disease but it is the part of COVID-19 disease which has persisted and we don't have a 'Reboot system' to tackle this immune dysregulation.

HCQ was tried initially for prophylaxis, treatment of COVID-19 due to its anti-inflammatory properties but has not shown any dramatic results. WHO has removed HCQ from treatment plan after many trials results with disappointing outcomes. HCQ is a drug with multiple beneficial pleiotropic effects such as immunomodulatory effects which regulates

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Conflicts of Interest: Nil
Research Funding: Nil

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