International Journal of Research in Medical Sciences
Deb S et al. Int J Res Med Sci. 2022 Jun;10(6):1390-1401
www.msjonline.org
pISSN 2320-6071 | eISSN 2320-6012

DOI: https://dx.doi.org/10.18203/2320-6012.ijrms20221501

Review Article

Diverse immunopathological manifestations and immunogenomic predispositions in COVID-19: summarizing the evidence

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Received: 24 April 2022
Revised: 12 May 2022
Accepted: 18 May 2022

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ABSTRACT

The COVID-19 pandemic has caused immense damage to most nations of the world, both in terms of loss of human lives, as well as, socio-economic attributes. The immunopathogenesis of the responsible pathogen, SARS-CoV-2, has been a focal point and researchers have succeeded in deciphering the multi-organ tropism of the virus along with its different routes of infection. The hallmark feature of the SARS-CoV-2 disease pathogenesis is the high rates of transmission and the susceptibility of a vulnerable group with systemic co-morbidities. Also, genetic components of the host, as well as mutant variants of the virus have further complicated the development of appropriate treatment strategies and preventive measures. The virus is aptly able to modulate the host immune system and mediate immune-dysregulation in terms of cytokine or chemokine production leading to a heightened inflammatory response. In the current review, we have summarized the present research on SARS-CoV-2 from the angles of host genetic polymorphism, genetic variants of the virus, and how these affect the high transmission, disease susceptibility, and tissue tropism in multiple organs of the human body.

Keywords: COVID-19, Immunopathology, ACE2, Phylo-immunogenomics, Hypercytokinemia, Hypercomplementemia

INTRODUCTION

An outbreak of a novel coronavirus disease (COVID-19; previously known as 2019-nCoV) was reported in Wuhan, China in December 2019, which subsequently spread to 26 countries worldwide.[1,2] Despite being a primary respiratory pathogen, SARS-CoV-2 has been reported to involve other systems too irrespective of age or health status of the infected individuals thereby confirming a multi-organ involvement of the virus.[3] Another hallmark feature of this virus is the ability to modulate the host immune response and affect the homeostasis of the anti-inflammatory and proinflammatory cytokines. The severity of the disease is not only attributed to the increased viral load but also the excessive plethora of cytokines and chemokines synthesized in the disease progression.[4] Moreover, according to recent reports, there is a variation in disease susceptibility in the patients with COVID-19 which points to the involvement of host genetic characteristics as well as genetic variants of the virus.[5] Demystifying the immunopathogenesis of the virus will help not only in formulating a model of its

pathogenesis but also develop therapeutic strategies to alter the immune response and promote better outcomes in COVID-19 patients with high-risk co-morbidities.[6]

Phylo-immunogenomics: a brief window into the future of the past

Viral entry: an outlook into early immune response homology

The entry of the virus inside the host cell results in an activation of the innate immune response along with the synthesis and secretion of a variety of inflammatory molecules. Interaction between specific viral components and pattern recognition receptors (PRRs) of the host immune system initiates cellular signalling pathways that lead to the production of various cytokines.[7,8] According to several reports, the entry of both SARS-Co-V and SARS-CoV-2 is mediated by angiotension-converting enzyme 2 (ACE2) whereas MERS-Co-V entry is mediated by dipeptidyl peptidase-4 (DPP4).[9,10]

During the outbreak of 2003 caused by SARS-Co-V, a systemic cytokine profiling in individuals suffering from the disease demonstrated higher concentrations of TH1 cytokines such as IFN-γ, IL-2, and IL-12 along with proinflammatory cytokines like IL-6, IL-1, MCP-1, IP-10, CXCL9/MIG, IL-18, TGF-β and IL-8.[11-15] Similarly, during another outbreak in the year 2012 caused by MERS-Co-V, blood cytokine analysis performed in severely infected individuals showed a marked rise in the concentration of IL-6, IL-10, IL-15, IP-10, IL-17, TNF and IFN-γ /α2 in comparison to controls.[16,17] Moreover, a significant increment in the mRNA expression of IL-8, IL-12, IFN-γ, RANTES, IP-10, MCP-1, and MIP1-α was observed in macrophages infected by MERS-Co-V.18 Furthermore, patients infected with SARS-CoV-2 showed elevated concentrations of peripheral blood immune mediators including MCP-1, IL-6, CCL8 (MCP-2), IL-7, IL-1β, MIP2-α (CXCL2), TNF-α, CXCL16, IL-1RA , IL-2, IL-9, MIP1-α, IP-10, IL-10, bFGF, MIG, G-CSF, IFN-γ, GM-CSF, MIP1-β, PDGF, IL-8, and VEGF.2,19-21 In contrast to SARS-Co-V, MERS-Co-V can also infect monocyte-derived-dendritic cells and macrophages.[18,22,23] Comparatively, common cytokines elevated in both MERS and SARS-COV-2 infection included IL-10, IP-10, IL-6, and TNF-α (Figure 1) and relatively altered MIG, IL-8, IL-1, MCP-1, and IL-2 levels were observed in both SARS-CoV-2 and SARS CoV infected patients.

A comparative outlook into the immunological interplay between coronaviruses

Based on in vitro data, there is a distinct pattern in the cytokine storm of COVID-19 with SARS-Co-V and MERS-Co-V infection.[24] Markedly, a set of three cytokines (IL-6, IP-10, and IFN-γ) was observed to be elevated in all three highly pathogenic HCoV infections (Figure 1). IP -10 levels correlated with disease severity among SARS-Co-V infected patients.[15] Moreover, higher levels of IP-10 were also linked with disease progression and poor prognosis in MERS-Co-V infection.[16] Cheemarla et al proposed that elevated levels of nasopharyngeal IP-10 could be used as a biomarker for undiagnosed COVID-19 indicating the importance of IP-10 signalling.[25] In addition, IL-6 results in the activation of the coagulation cascade, conversion of naive T cells, increase in vascular permeability, and reduced cardiac function, contributing to the increased disease severity.[26,27] SARS-Co-V infected patients displayed higher levels of IL-6 which correlated with the disease progression.[14] Based on accumulative observations, it is feasible that an increased response of TH1, TH2 cytokines along with proinflammatory chemokines contributed to the immune pathology of COVID-19 infection, in contrast to SARS-Co-V which was predominantly mediated by IFN-γ induced TH1 response.[24,28]

Immunogenomic predispositions and different systemic responses in COVID-19

Much of the severe illness associated with COVID-19 is believed to be the result of a hyper-inflammatory process as described earlier.[29] The phenomenon has been implicated in critically ill patients infected with SARS-CoV-2.6 The cytokine storm appears pivotal to the development of some of the severe presentations of SARS-CoV-2 infection: acute respiratory distress syndrome (ARDS), thromboembolic manifestations like ischemic strokes caused by large vessel occlusion and myocardial infarction, encephalitis, acute kidney injury, and vasculitis (Kawasaki-like syndrome in children and renal vasculitis in adult).[6]

Pulmonary manifestation in COVID-19 from an immunogenomic perspective

Pulmonary manifestations in COVID-19 infection

Based on clinical severity, COVID-19 disease has been stratified into three stages.[30,31] The first stage is the stage of pulmonary infection with SARS-CoV-2. In this phase, the patient presents with generalized malaise, fever, and flu-like symptoms. Over time, some patients develop viral pneumonia with pulmonary infiltrates; some may require respiratory support. The second stage is also complicated by pulmonary inflammation and coagulopathy, either concurrently or one following the other. Moreover, increased levels of inflammatory molecules such as C-reactive protein (CRP), ferritin, IL-6, IL-1, and D-dimer are associated with the development of ARDS and an overall poor outcome.[31,32] Finally, the third stage of the disease is characterized by fibrosis.30 Grossly, the lungs often had increased weight, congested parenchyma, necrosis, haemorrhage, and embolic changes.[30,33]

Cytokine burst and immunogenomics predisposition behind pulmonary manifestation

IL-1β and its related family-members (IL-18, IL-33) are key players in diffuse alveolar damage and are known to recruit immunocytes and stimulate further cytokine generation. The primed immunocyte counters multiple stimuli, in the form of PAMPs, or DAMPs to stimulate the secretion of a biologically active IL-1β molecule. IL-1 receptor signalling induces an acute inflammatory response, activating a series of downstream immunocytes, and causes severe damage to the pneumocytes.[34] A study revealed that IL-1 transcription preceded any other cytokine production, indicating the role of IL-1 as an initiator of the cytokine storm.[34] IL-1ß and TNF-α regulate Th-17 cell development and functioning. The cytokines released by Th-17 cells, viz. IL-17 and GM-CSF are also significantly raised in patients of severe COVID-19.[35]

Pulmonary alveolar macrophages (PAMs) are hypothesized to be the pivotal players in the immuno-pathogenesis of cytokine storm in SARS-CoV-2 infection. Tay et al proposed that the monocyte-macrophage series of immunocytes elicit the onset of severe COVID-19 disease by the release of mediators like MCP-1, IP-10, and MIP-1α.[36] These reticuloendothelial cells can produce large amounts of pro-inflammatory cytokines.[37] The cells had a greater secretion of IL-6 and GM-CSF, suggesting a central position in the advent of cytokine storm.[37] HLA-DR expression on CD14+ monocytes of COVID-19 patients was found to be significantly low among severe cases when compared to mild cases, the levels of which improved on treatment with IL-6 inhibitor (Tocilizumab).[38] A higher level of CCL-2 was also seen in the serum of SARS-CoV-2 patients which is a known chemokine for monocyte.[38]

Immunogenomic interplay behind altered cardiovascular parameters

Accumulative pieces of evidence suggest that cardiovascular manifestations including myocardial injury, pericardial effusion, infective endocarditis, endothelitis, heart failure, arrhythmias, and venous thromboembolism are common in patients with COVID-19, especially in those with severe disease.

Cardiovascular manifestations in COVID-19

A case series of three patients with COVID-19 have shown endothelitis with viral particles in endothelium and a large concentration of apoptotic bodies in numerous organs including heart, lungs, and small bowel.[39] Direct viral damage was the proposed mechanism.[39] According to a study, 22.7% patients with COVID-19 suffer from deep venous thrombosis (DVT).[40] This might be due to a higher level of D-dimer, fibrin degradation products (FDP), and fibrinogen among COVID-19 infected individuals as compared to healthy controls.[41] A summary of two cases of COVID-19 illustrates the development of acute pulmonary embolism evident on CT-pulmonary angiogram in both of them.[42]

Hyperinflammatory response behind Cardiovascular insults in COVID-19

Several studies have established the systemic elevation of cytokines such as IL-2, IL-6, IL-10, GCSF, IFN-γ, MCP-1, MIP-1α, and TNF-α likely contributes to cardiac injury in a situation analogous to cardiotoxicity in the setting of chimeric antigen receptor (CAR)-T cell therapy. A prior study documented that in a cohort of 137 patients with post-CAR-T cytokine release syndrome (CRS), 21% had elevated troponin, and 12% developed cardiovascular events including cardiac arrest, decompensated heart failure (DHF) and arrhythmias.[43] It was noted that a shorter time from CRS onset to the administration of IL-6 inhibitor, tocilizumab, was associated with a lower rate of cardiovascular events.[44] Notably, tocilizumab may have some benefits in COVID-19 infection suggesting a common mechanism of injury in the two settings.[45] Furthermore, membrane translocation of ADAM17 leads to a reduction in myocardial ACE-2 levels and activity which is associated with an increase in plasma ACE-2 activity. Thus, increasing ADAM17 levels and/or activity to enhance ACE-2 shedding and increase soluble/plasma ACE2 levels could be a way to block SARS-COV-2 entry into cells.[46]

Neuroinflammatory and neuro-autoimmune manifestation in COVID-19

The systemic inflammation along with neuroinflammatory changes in patients with COVID-19 are associated with increased upregulation of brain proinflammatory molecules, dissociated neuroglial reactivity, and subsequent pathological remodelling of neuronal, neuroglial, and neurovascular networks.[47] Cerebral hypoxia secondary to COVID-19 may overproduce proinflammatory transcription factors including NF-Kβ and HIFs which may trigger glial cell reactivity, induce mitochondrial oxidative damage and eventually synaptic loss, demyelination like changes, and neuronal death.[44] Molecular mimicry between viral antigen and myelin basic protein may form the basis of several autoimmune demyelinating syndromes observed in COVID-19. In addition, dysregulation of ACE-2 receptor and spike surface glycoprotein may play crucial roles in neuro-autoimmune syndromes, particularly encephalomyelitis, related to COVID-19.[48]

Among the autoimmune PNS manifestations, GBS has drawn significant attention from clinical neurologists so far.49 Both demyelinating, as well as axonal variants of GBS, have been reported in the context of COVID-19.[49] Additionally, it is observed that none of the polyradiculitis cases associated with COVID-19 revealed the presence of SARS-CoV-2 in CSF - an observation compatible with the immune mechanism of radiculo-neuropathy rather than direct viral invasion.[50] In the acute inflammatory demyelinating subtype (AIDP), the target epitopes in Schwann cells result in demyelination while the acute motor axonal neuropathy (AMAN) subtype, the immune

response is against components of peripheral nerves (gangliosides GM1, GD1a, and GalNac-GD1a) causing axonal degeneration.[51]

Among the CNS manifestations of COVID-19, cases of autoimmune encephalitis have been reported by clinicians. Panariello et al have described a case of COVID-19 related encephalitis that was found positive for anti-NMDAR antibody.[52] Pilloto and colleagues have documented a case of steroid-responsive encephalitis indicating immune-mediated pathology behind the occurrence of encephalitis.[53] In addition, cases of hemorrhagic encephalitis have been documented by clinicians dealing with SARS-CoV-2 infected patients.[54] Although a definite link with auto-immune pathology has not yet been established in these cases, its possibility has been duly considered by the authors of these papers. Spinal cord demyelination, both para- and post-infectious, as a form of autoimmune CNS manifestation have also started to surface up in contemporary literature.[55] It is observed that dorsal cord involvement is relatively more frequent in COVID-19 related myelitis, and in most cases, it is in the form of long segment myelitis. Associated antibodies have mostly been reported to be negative in this context. Similar to polyradiculitis, SARS-CoV-2 has been rarely detected among the documented COVID-related myelitis cases, implicating immune-mediated mechanisms.[55]

Several other case reports and studies have also documented increased incidences of neuropsychiatric disorders associated with variable severity of COVID-19.[56] Mild to moderate infection with SARS-CoV-2 may promote cognitive disorders with the emergence of delirium, acute psychosis, exaggeration of mild cognitive impairments, or with acceleration of dementia associated with various other neurodegenerative disorders including Alzheimer's disease, Parkinson's disease and Multiple sclerosis.[57] Numerous findings suggest the role of cytokines and predisposing neuro-immunogenomics behind different behavioural and emotional manifestations via interaction with specific brain areas and neuronal microarchitecture.[44] Severity of COVID-19 has been invariably associated with host immune response mainly significant elevation of IL-6 which may directly or indirectly correlate with disease progression and overall outcome. Interestingly, astrocytes and microglia are mainly responsive to IL-6 and may enhance IL-6 and other pro-inflammatory cytokines in response to pathogenic invasion.[58] Intriguingly, dynamic changes of IL-6 in both plasma, as well as CSF, are implicated in the onset of major depressive disorder (although several other factors could be important contributors).[59,56] Besides, IL-6 elevation has also been correlated with suicide endophenotype behaviors such as personality disorders, aggressivity, and impulsivity.[59] While elevation in IL-1β, TNF-1α, IL-6, IFN-γ level has been found significant in the acute phase of bipolar disorders and parallel decrement of anti-inflammatory factors like IL-10 and TGF-β1 has correlated with the manic phase.[60]

Noteworthy to mention that IL-1 elevation is evident in plasma as well as in CSF of different epileptic phenotypes suggesting potential seizure-inducing properties of cytokines though the direct association between epilepsy and COVID-19 have not yet been reported.[61,62] However, the American Epilepsy Society suggested that COVID-19 could aggravate the risk of sudden unexpected death in epilepsy or SUDEP.[63]

COVID-19 mediated renal inflammatory insults

Renal parameters have been found altered in patients with COVID-19 which undoubtedly play a key role in overall prognosis and mortality. SARS-CoV-2 has been widely reported to result in proteinuria, hematuria, and acute kidney injury (AKI) from initial reports from Wuhan, China.[64] A recent multicentric observational study comprising of a cohort of 5700 patients from New York reported the requirement of renal replacement therapy in 3.2% of patients.[65] Additionally in-hospital mortality was significantly higher in patients with proteinuria, hematuria, elevated baseline creatinine, blood urea nitrogen and AKI stage 2-3.[66] The first histological analysis of 26 post-mortem patients with COVID-19 from China reveals evidence of acute tubular injury (ATI), collapsing glomerulopathy (CG), renal vascular injury, and podocyte foot process effacement.[67] Gross et al reported findings of COVID-19 associated nephritis with a contrasting report depicting low antithrombin-III level and severe hypoalbuminemia (between 1.4-1.9 mg/dl) in severe patients in ICU, whereas mild to moderate group of patients in normal ward had the best serum albumin results (>2.5 mg/dl) and normal urine.[68] Another three reports published, one of which is associated with tubuloreticular inclusion (an indicator of viral replication and subsequent interferon upregulation) within endothelial cells, and spherical particle resembling virions within podocyte cytoplasm; suggesting a possible hypothesis of direct cytopathic effect of the virus, like in HIV associated glomerulopathy.[69] Interestingly, a post-mortem study by Diao et al reveals enhanced complement activation and membrane attack complex or C5b-9 deposition in tubules compared to its deposition in glomeruli and capillaries, whereas normal kidney tissue did not show such findings.[70] Henceforth, it can be interpreted that COVID-19 mediated hypercomplementemia may aggravate the damage in renal filtration architecture and may induce tubular injury and accelerate microvascular atherothrombotic events.

Still, the exact mechanism behind the foot process injury is debatable but is likely to be associated with multiple immunological pathways corresponding to specific immunogenomic predispositions. Parallel studies in non-COVID-19 minimal change disease (MCD) have revealed a profound imbalance in T-cell populations during the initial stage of the disease with a majority of Th-2 cell cytokine profiling (IL-4,5,9,10 and 13) which can hypothetically correspond to COVID-19 mediated 'cytokine storm'.[71] Evidentially MCD responds to B-cell

depletion therapy viz- rituximab (anti-CD-20 monoclonal antibody).[72] Of interest, Angeletti et al through a cohort of 159 pediatric patients with nephrotic syndrome reported that chronic immunosuppression therapy (preferentially B-cell depleting therapy) could be beneficial as well as prophylactic in children and young adults in SARS-CoV-2 containment areas and it does not correlate with the risk of COVID-19.[73] Several other studies have emphasized the importance of continuous renal replacement therapy (CRRT) in effective management of COVID-19 mediated hemodynamic instability and multi-organ failure. Filters with membranes made of acrylonitrate, sodiummethallyl sulfonate plus polyethyleneimine, and new sorbent cartridges designed to expel circulating cytokines and inflammatory mediators could also be incorporated.[74]

Other immune mechanisms like immune complex deposition in glomeruli can lead to COVID-19-mediated glomerulonephritidis. Another newly emerging factor, high-risk APOL1 genotype has been described in relation CG arising in the backdrop of COVID-19 in many patients of African-American ancestry.[75]

COVID-19 behind dissociated immuno-endocrinological homeostasis

COVID-19 infection has established a significant impact on the metabolic axis via its interaction with the immune cytokine interaction.[76] SARS-CoV-2 accomplishes its entry via the ACE2 receptor which is found to be expressed in both endocrine and exocrine pancreas.[77] The destruction of insulin-producing beta cells of the pancreas was documented as a plausible mechanism in the development of acute diabetes during the SARS outbreak and some reports suggest that SARS-CoV-2 can also be a potential trigger for the development of type-1 diabetes mellitus (T1DM). This novel coronavirus mediates the destruction of beta cells of pancreas via release of TNF-α, IFN-γ and some proinflammatory cytokines such as MCP-1, IP-10.[78,76] But we have limited data to suggest whether it is a direct virus-mediated destructive insult or secondary to an autoimmune trigger by the virus. Such a situation may manifest clinically with diabetic ketoacidosis (DKA/HOS) with significant intravascular and extravascular volume contraction which may have significant implications in patients with severe COVID 19 infection with/without ARDS.[79] DKA/HOS, brittle control and more frequent hypoglycemia has been reported.[79] Prognosis and relation with disease severity needs to be seen in patients with good and poor control of the glycemic status.

Moreover, SARS-CoV-2 may play an important role to worsen the condition of patients with insulin resistance or pre-existing type 2 diabetes (T2DM).[76] According to existing literature, COVID-19 infected patients with underlying diabetes mellitus (DM) express downregulated ACE2 and a higher amount of inflammation related biomarkers (serum ferritin, C-reactive Protein, IL-6) which make them susceptible to develop acute respiratory distress syndrome (ARDS).[80] In addition, an evidential increase in pro-inflammatory cytokines (IL-1β, TNF-α, MCP-1) explains a plausible mechanism behind the deterioration of DM patients.[76]

During the previous epidemic, a hypothesis on molecular mimicry stated that certain amino acid sequences were similar to adreno corticotrophic hormone (ACTH) which caused an inhibition of cortisol rise upon stress induction. Therefore, based on the homology it can be assumed that the SARS-CoV-2 infected patients may develop a critical illness-related corticosteroid insufficiency due to 'molecular mimicry'.[81] Nevertheless, another study showed patients with pre-existing adrenal insufficiency are at higher risk to manifest lower-respiratory tract infections.[76] Steroid dosage may need to be increased more than a mere doubling of the steroid dose used in stress.[76] Parenteral hydrocortisone should be started in patients with significant hypovolemia, hypotension. Adrenal involvement may also occur suddenly as a result of DIC and associated destruction. The incidence of hypocortisolic state needs to be seen in COVID infection and whether steroid replacement alters the prognosis in such patients. Subclinical adrenal insufficiency needs to be suspected in patients with refractory hypotension, hyponatremia, unexpected hyperkalemia but whether steroid therapy alters the natural history of the disease is yet to be known.

According to a study by Mc Chen et al, 56% (28/50) of a total of 50 COVID-19 infected patients showed a TSH level lower than normal.[82] Interestingly both TSH and serum TT3 were significantly lower in patients with COVID-19 than those of the healthy control group and non-COVID-19 pneumonia-associated patients which reveal a positive correlation between the COVID-19 severity and TSH/TT3 level.[82] Whether levothyroxine will have any potential benefit on clinical outcome and mortality is yet to be known. Alternatively, thyrotoxicosis might be associated with SARS-CoV-2 directly infecting the thyroid glands as described in other viral infection in form of subacute thyroiditis (SAT); characterised by self-limiting thyrotoxicosis of variable duration.[83] According to a case report by Brancatella et al, an 18-year-old female who had been previously diagnosed with COVID-19, presented with symptoms of SAT including palpitation as well as neck and thyroid pain after a period of 18 days (completely recovered from COVID-19). Her T3 and thyroxine (T4) levels were markedly elevated along with raised inflammatory markers like erythrocyte sedimentation rate (ESR), CRP, thyrotropin receptor autoantibodies (TSHRAb), thyroid peroxidase antibodies (TPOAb).[80] But what is at the root of connection between COVID-19 and SAT. This in fact obviously needs more research. Still it can be speculated that a positive correlation exists between viral infection or a post-viral inflammatory reaction in genetically predisposed individuals. HLA-haplotype mainly HLA-Bw 35, but also HLA B67, HLA-B15/62, and HLA-Drw8 have been reported to augment predisposition towards SAT.[84]

Another case series by Salat et al, has also reported a finding of post-infectious autoimmune hyperthyroidism or Grave's disease in a 53 years old female who had been diagnosed with COVID-19 a month earlier since her new onset symptomatic presentations of persistent asthenia and tremor with palpitation while her thyroid function revealed suppressed serum TSH with elevated serum free T4 (FT4). TRAb as well as TPO and thyroxin binding globulin (TGB) autoantibodies were also positive along with evidentially increased iodine uptake. Hence, based on these initial pieces of evidence, SARS-CoV-2 might act as a possible trigger towards latent or a new concept of autoimmunity in form of both SAT as well as Grave's disease.[85] Alterations in thyroid function may occur as part of non-thyroidal illness (NTI) in its various forms or as a result of direct involvement of virus mediation destruction or trigger of the autoimmune mechanism.[83] Whether LT4 supplementation is going to have any benefit or alter the natural history and mortality is yet to be known and is a matter of conjecture.

Interestingly, both the hypothalamus and pituitary express ACE2 receptor and both of these can be a potential target for the virus.[76] According to a study by Leow et al, SARS-CoV infected patients showed central hypocortisolism during post-recovery whereas a majority of them got recovered within a year.[86] It is unlikely that the hypocortisolic state is secondary to persistent hypopituitarism but possible stress-mediated suppression of the hypothalamus-pituitary axis (HPA). Currently, very limited data is available to make a certain correlation between COVID-19 infection and hypothalamo-pituitary axis. Though from the phylogenetic point of view, it can be assumed that SARS-CoV-2 may affect hypothalamo-pituitary axis directly or via immune-mediated hypophysitis. Anterior pituitary involvement may occur secondary to disseminated intravascular coagulation. Prolactin is an inflammatory-immune marker and low prolactin has been associated with poor recovery and increased mortality in COVID-19.[87,88]

Miscellaneous immunopathological manifestations in COVID19

SARS-CoV2 infection may have direct cytopathic effects on the endothelium and dermal vessels and this has been described in vesicular or papular–vesicular lesions.[89] The ACE2 receptor mediating viral entry to cells has been demonstrated in the skin and adipose tissue as well. Adipocytes can serve as a viral reservoir.[90] The immune response to infection may cause Langerhans cells activation, resulting in vasodilation and spongiosis. Keratinocytes may be a secondary target after Langerhans cells activation, inducing a spectrum of clinical manifestations.[91] The currently recognized dermatological manifestations have been classified into 4 clinical patterns: exanthema (varicella-like, papulovesicular and morbilliform rash), vascular (chilblain-like, purpuric/petechial and livedoid lesions), urticarial, and acro-papular eruption.[92] These symptoms can be correlated with graded severity of COVID-19 infection, from chilblain-like lesions in milder disease to livedo in the most severe cases.[93] Existing literature suggests that generalized macular or maculopapular exanthem (morbilliform) is the most common cutaneous manifestation in COVID-19, which appears concomitantly with other symptoms of infection and lasts for about 3-10 days, with itching in most cases.[91] Both COVID-19 associated purpuric and petechial lesions, and livedoid/necrotic lesions; typically seen in adult patients, may appear at any point in the disease course, the former mostly localized on the trunk, buttock, limbs and the latter ones on the limbs with a more severe disease course.[92] Isolated incidents of COVID-19 associated immune thrombocytopenic purpura, antiphospholipid antibody syndrome, and Kawasaki disease have also been described.[94-97] A case of histopathologically confirmed cutaneous small-vessel vasculitis (CSVV) in a SARS-CoV-2 positive patient has also been documented.98 Cases of acral papular eruption and urticaria (presenting as slightly disseminated erythematous skin rash) associated with SARS-CoV-2 have also been described.[92] Lastly, skin manifestations due to cutaneous adverse reactions to drugs prescribed for treatment of COVID-19 are to be considered. Whether SARS-CoV2 infection can directly cause a worsening of chronic inflammatory diseases such as psoriasis or atopic dermatitis remains to be determined.[92]

According to various studies, gastrointestinal symptoms are commonly seen with COVID-19 infection. Incidence of diarrhea ranges from 2%-24% among COVID-19 patients.[2,99-102] A pooled meta-analysis showed 7.4% COVID-19 patients reported diarrhoea and 4.6% reported nausea and vomiting.103 In a study mRNA sequence analysis was done to determine gene expression changes caused by SARS-CoV and SARS-CoV2.[104] SARS-CoV2 elicited a broader immune response than SARS-CoV. It also showed SARS-Cov-2 productively infect human enterocytes. Primary enterocyte progenitors are primary targets of gut infection. SARS-CoV2 RNA has also been detected in esophagus, stomach, duodenum, and rectum specimens in a recently published study.[105]

The interactions between enteric nervous system and central nervous system may suggest alternative routes of neuroinvasion which should be explored further. Interestingly, a study reported that SARS-CoV-2 infection instigates an inflammatory response in the gut. Patients with diarrhoea displayed elevated fecal calprotectin (FC) and it significantly correlated with serum IL-6 levels.[106] Accumulative evidences suggest that inflammatory response is generated with the release of proinflammatory metabolites when the virus reaches the gut. This is how the gastrointestinal tract is infected in COVID-19. Proinflammatory metabolites can reach the brain through the vascular or lymphatic system. Intestinal inflammation can affect cognition through the vagus nerve.[107] EGCs are antigen-presenting cells, they express MHC-II and respond to harmful stimuli mainly through Toll-like

receptor-2 and 4, thus it protects the host against gut pathogens and regulates the neuroimmune axis. EGCs are present in Gut associated Lymphoid tissue (GALT) and various interactions lead to differentiation of CD4+ to different subtypes. EGCs are activated by viruses or their antigens, this leads to the release of IL-6 and other inflammatory mediators. The peripheral neurological priming of immune response by viruses is a key step and explains for later onset of neurological complaints through a gut-brain axis. B cells, mast cells, neutrophils and other immune cells participate and release IL-1β, NLRP3, CXCL2, CXCL16, NFaR1, IL1a, IL1b, IL2, IL12, IFN-γ, TNF-alpha which can reach hematogenously to the brain. The virus also directly reaches the brain through blood. The virus can also reach the brain by the enteric neurons traveling through dorsal root ganglion to the brain. In the brain, the virus and its proinflammatory cytokines lead to the maturation of microglia and activation of astrocytes leading to a cascade of neuroinflammation and neurodegeneration through the release of TNF, cytokines, ROS, and other inflammatory mediators decreasing the survival of neurons. It can also affect the cardiorespiratory centre in the brain which can be a possible explanation of respiratory failure.[108-110]

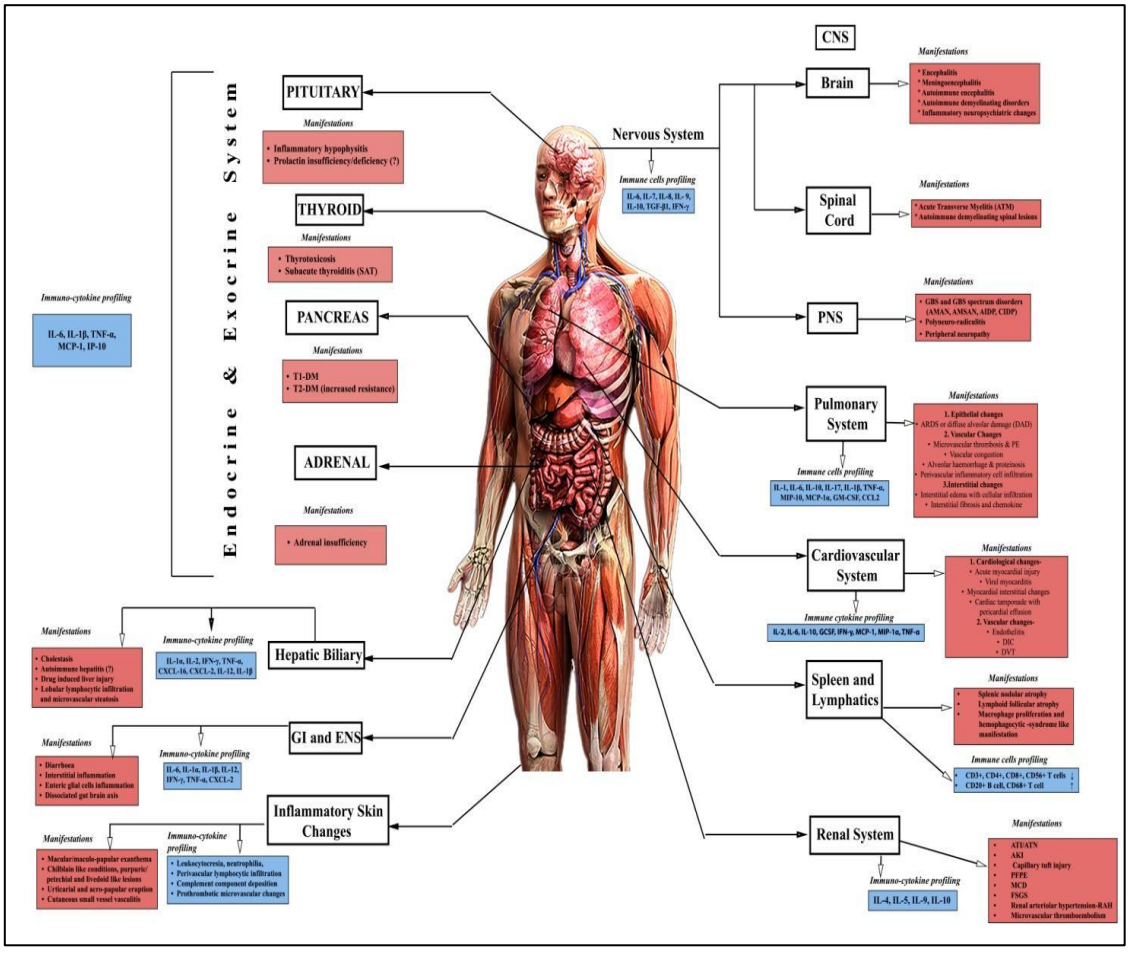

Figure 1: SARS-CoV-2 infection leads to a streamlined elaboration of specific cytokines and recruitment of dedicated lineage of immunocytes that manifest as a multisystem disease, involving but not limited to the nervous system, lungs, heart, blood vessels, spleen, liver, kidneys, alimentary tract, endocrine organs, and integuments.[24,31,32,40-42,47-49,55,66-68,82,86,92,103,117]

It is intriguing to know about the pattern of liver involvement in COVID-19. Given the enhanced ACE-2 expression in cholangiocytes but not necessarily in hepatocytes; liver could be a major target. Hepatic involvement in COVID-19 could be related to the direct cytopathic effect of the virus, an uncontrolled immune reaction, sepsis, or drug-induced liver injury.[111,112] With the available evidence, it is quite clear that elevated liver enzymes are observed predominantly in severe as well as in critical cases of COVID-19.112 It is still unclear whether the elevated liver enzymes (AST, ALT, and GGT) were primarily due to the disease or drug-induced liver injury but there is a possible effect of liver damage due to inflammatory cytokine storm in severe COVID-19.[113] Interestingly despite the excess presence of ACE2 in cholangiocytes, more patients are found with elevated transaminases .112 It is even difficult to say if COVID-19 aggravates cholestasis in patients with primary biliary cholangitis (PBC) and primary sclerosing cholangitis (PSC) requires further analysis.[114] Peripheral blood examination of COVID-19 patients revealed significantly

reduced but hyper-reactive CD4 and CD8 cells in a pro-inflammatory state, with increased CCR6+ Th17 CD4+ T cells and cytotoxicity granulations in CD8 cells, which may also contribute to hepatocellular dysfunction.[115] Another report by Tian S et al showed that post mortem liver biopsy in four COVID-19 patients reveals mild to moderate sinusoidal dilatation along with focal micro-vescicular steatosis and lobular lymphocytic infiltration. Keeping these findings in mind, it is possible that hepatic dysfunction may result from 'cytokine storm' rather than the direct cytopathic effects of the virus. Though more studies are required to ascertain the pattern and the degree of liver injury in these patients during the natural course of the disease.[116]

Spleen is postulated to be one of the organs directly attacked by the virus in some patients who died from COVID-19.[117] T and B lymphocytes in the spleen decrease in varying degrees, lymphoid follicles are atrophied, decreased or absent, and the number of NK cells do not change significantly. The tissue changes in the spleen are not related to the use of low dose corticosteroid, and probably reflect the direct effect of viral pathogenesis or altered immune response.[118] Xu X et al described the associated splenic changes in ten patients with COVID-19 disease. In one subgroup of the patients the cellularity of the spleen decreased, white pulp atrophied at different levels and lymphoid follicles were decreased or absent; moreover, the ratio of red pulp to white pulp increased with varying degrees.[118] In a smaller subgroup, spleen showed neutrophilic or plasma cell infiltration, macrophage proliferation and hemophagocyte syndrome like manifestation.[118] Immunohistochemistry revealed that the T and B lymphocytes of the spleen in all cases reduced in varying proportions. CD20+ B cells were found to accumulate in the lymphoid sheath around the splenic artery in 8 cases. CD20 and CD21 immunostaining in 2 cases showed that the number of white pulps was almost normal, but splenic nodules were atrophic. CD3+, CD4+ and CD8+ T cells were also decreased. In 9 cases, CD68+ macrophages revealed no significant changes in the distribution and number. While more CD68+ cells were found in the medullary sinuses of 1 case (related to fungal infection), only few CD56+ cells were found.[118]

CONCLUSION

Immunogenomics and subsequent diverse immunopathological responses are the main pivotal points for the overall disease prognosis in COVID-19 and the possible underlying mechanisms that contribute to exacerbating patient outcome could be adopted to tackle the disease and its complications. The identification of such immunogenomic determinants would be crucial to correspond priorities in clinical management strategies and to isolate genetically "high risk" individuals, including the health care workers. Besides, population immunogenomics and phyllo-immunogenomic relationships could be useful assets in deeper understanding as well as in adopting strategic ways towards taking preventive measures of viral spreading. Looking back at the immunological aspects of the previous two outbreaks, it is quite clear that SARS-CoV and MERS-CoV use multiple strategies to avoid immune responses. The antigen presentation is one such avenue that gets affected by the coronavirus and the gene expression related to antigen presentation is downregulated after MERS-CoV infection; therefore, destroying the immune evasion of SARS-CoV 2 is imperative in its treatment and specific drug development. Population immunogenomics introspect on diverse outcomes due to genetic variants, which can be a pivotal step to help personalized and predictive medicine in the high-risk individuals. Based on the current knowledge, the cytokine storm appears to be the most dangerous and life-threatening event related to COVID-19 severity, mortality, and sustenance of major clinical consequences. The immune-mediated events related to SARS-CoV2 infection and the role of chemokine and cytokine receptor system will be the ultimatum and the final frontier towards targeted therapy and treatment strategies. On this basis a "immunogenomic risk-score" could be established that would be applicable to a large population and, so, it might be then possible to screen and selectively identify subjects carrying a combination of alleles of ACE2, ADAM17, and TMPRSS2 in conjugation with immunogenomic factors, conferring risk percentage of contracting SARS-CoV2 infection in individuals. Hence such a prospective immunogenomic approach to COVID-19 risk score assessment could complement ongoing GWAS investigations, exploring the whole DNA variations in these patients to address interindividual differences in COVID19 severity. Until now the genetic especially the immunogenetic influences on COVID19 prognosis and outcomes have largely been underestimated, thus we expect that this critical review might be able to fill the gaps and pave the way towards confirmatory investigation at both the translational and clinical levels.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: Not required

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Cite this article as: Deb S, Mondal R, Lahiri D, Ganguly U, Shome G. Diverse immunopathological manifestations and immunogenomic predispositions in COVID-19: summarizing the evidence. Int J Res Med Sci 2022;10:1390-401.