

Lymphocytopenia and COVID19: A Literature Review

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ABSTRACT

The novel coronavirus SAR-CoV-2 has resulted in huge wave of worldwide fear by its contagious nature, virulence and high mortality. Persistence condition of the disease with T-cells and Natural killer cells exhaustion leads to Lymphopenia or Lymphocytopenia. Lymphocytopenia is a condition of low lymphocyte count in the blood. Lymphocytopenia is an important adverse effect of COVID-19 as well as negative prognostic marker in many malignancies. It leads to hyper activation of immune system that can cause immunosuppression and promote cytokine storm that eventually leads to multi-organ failure and death. Restoration of lymphocytes and its function would be helpful to boost the immune response against COVID-19 disease. This review analyses the possible causes that may lead to the lymphocyte reduction in COVID-19 patients, and highlighting the possible therapeutic strategies that will help to control and prevent lymphocytopenia in COVID-19 patients.

KEYWORDS: COVID-19, SAR-CoV-2, T-lymphocytes, NK cells, Lymphocytopenia, cytokine storm

INTRODUCTION

The newly evolved Coronavirus disease is rapidly spreading throughout the world and has become the global health threat. Coronavirus disease (COVID-19), an acute respiratory disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which emerged in late 2019. It is marked as the third severe and readily transmissible disease to emerge in the 21st century. (1) The outbreak was first identified in Wuhan city of China on 12th December 2019. In the recent decades human respiratory system is facing an ongoing threat of various respiratory infections including Severe Acute Respiratory Syndrome coronavirus (SARS-CoV) which was detected first in China on 2002 (transmitted from Civet cats to humans) (2,3), swine-origin pandemic (H1N1) influenza A virus was detected first in the Mexico city of the United States and spread quickly across the United States and the world in 2009 (transmitted from swine pig to humans) (4), and the Middle East Respiratory Syndrome coronavirus (MERS-CoV) which was detected first in Saudi Arabia in 2012 (transmitted from dromedary camels to humans) (5) SARS, MERS and presently SARS-CoV-2 belongs to the family coronaviridae, and leading to heterogeneous group of disorders from the common cold to severe and life-threatening diseases. SARS-CoV-2 is considered to be one of the members of the CoV family that infect humans however this novel virus is genetically distinct. Phylogenetic analyses have revealed that Coronavirus is potentially zoonotic in origin followed by human-to-human transmission. Recent studies have shown that lymphocytopenia is found frequently among patients with COVID-19. These features could reveal that the adjusted immune system plays a key role in determining disease progression.

Host Response to COVID-19 Infection

Our immune system helps to control the viral infection by eliminating the pathogen and protecting our bodies from immune-related damage. However, its uncontrolled reactions may lead to immunopathogenesis. SARS-CoV-2 invades host human cells by binding to the angiotensin-converting enzyme 2 (ACE2) receptor. (6) ACE2 is a type 1 membrane protein which plays a key role in the Renin Angiotensin system (RAS) and target for the treatment of cardiovascular diseases. ACE-2 degrades Angiotensin II to generate Angiotensin 1-9. ACE2 also provides a direct binding site for the S-protein of coronaviruses. (7) SARS-CoV-2 possesses a nucleocapsid formed by genomic RNA, nucleocapsid (N) protein and further surrounded by an envelope (E). The helical capsid is covered by structural proteins: the proteins involved in viral assembly are the membrane protein (M) and envelope protein (E); the protein that mediates viral entry into host cells is the spike protein (S). Hemagglutinin-esterase (HE) are also encoded by some coronaviruses. (8) During coronavirus entry, initial critical steps include: Receptor binding that is the S1 subunit of the Spike protein binds to the ACE2 receptor on the host cell surface for viral attachment and Membrane fusion that is the S2 subunit of the spike protein fuses the viral and host membrane releasing viral RNA into the host cells (9) These viral RNAs are identified by the cytosolic viral RNA sensors such as retinoic acid-inducible gene-1 (RIG-I) / Melanoma differentiation associated gene 5 (MDA5) (10) and Toll-like receptors (TLRs)-3,-7 located in the endosome compartment. TLR-3 recognizes viral double-stranded RNA whereas TLR-7 recognizes viral single-stranded RNA. Activation of these cytosolic viral RNA sensors triggers the downstream signal

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transduction, with production of innate pro-inflammatory cytokines (IL-1, IL-6, TNF- α) and type I IFN- α/β , which are essential for anti-viral responses.(11) Type-1 interferons (IFN-I) are group of interferon proteins comprising the ubiquitous α and β subtypes as well as the ϵ , ω and κ subtypes. They play crucial role in viral replication and spread by declining the rate of cell metabolism or by secretion of cytokines which promote the activation of the adaptive immunity(12) Continuous viral replication leads to delayed IFN-1 signalling and promotes the accumulation of macrophages and neutrophils to various tissues resulting in elevated levels of proinflammatory cytokines.(13) When COVID-19 breaks out, the total number of neutrophils and lymphocytes, which generate uncontrolled viral replication in early stages of infection, could be changed(14)

Lymphocytopenia and covid-19

Cytotoxic lymphocytes such as cytotoxic T lymphocytes (CTLs) and Natural killer (NK) cells plays critical role in modulating the immune response. The functional exhaustion of cytotoxic lymphocytes is correlated with disease progression. Preliminary studies in COVID-19 patients with severe infection suggests a reduction in NK cell number and function, resulting in decreased clearance of infected and activated cells, and unchecked elevation of tissue-damaging inflammation markers. Another study reported that severe cases of Covid-19 patients have low lymphocyte counts and have higher risk of death from the infection. (15) Lymphopenia or lymphocytopenia is a condition of reduced blood lymphocyte levels. Evidences shows that on the onset of the infection severe patients had increased T-cells and CD4+ cells due to their impaired function by SARS-CoV-2 which is followed by rapid depletion of cytotoxic CD8+ T-cells. Low lymphocyte count was observed among severe cases of COVID-19 infection as compared to non-severe cases.(16,17)

Exhaustion of T-CELL or Lymphocytes

Lymphocytes or T-cells is a major component of our immunity system consisting of CD4+ helper T-cells and Cytotoxic CD8+ T-cells. Both CD4+ and CD8+ possess an antigen-recognition T-cell receptor (TCR). CD4+ and CD8+ T cells evoke in response to viral invasion and resolve the viral infection by proliferation of tumor necrosis factor-Alpha, interleukin -2, interferon-gamma and cytotoxic mediators followed by cell contraction and persistence of the memory pool. However, continuous exposure of CD4+ and CD8+ cells to the viral antigens during the viral infection these cells undergo functional defect and an associated increase in the expression of coinhibitory receptors. This phenomenon termed as T-cell or lymphocyte exhaustion. Exhausted cytotoxic T lymphocyte cells lose their ability to produce cytokines, capacity to proliferate, cytotoxicity required for killing virus-infected cells, and effective memory cell generation. Instead, these exhausted T-cells with high expression of inhibitory immune checkpoints render patients unable to mount an effective CTL response against Covid-19 viral infection(18). Moreover, the up regulation of the inhibitory receptors (e.g., NKG2A) is associated with the exhaustion of NK cells and CD8+ cells in the Covid-19 patients. Interestingly, in patients recovering after therapy, the number of NK and CD8+ T-cells was restored, and simultaneously their NKG2A expression was markedly reduced (19). Limited function of exhausted T-cells may also be associated with the increased expression of immune-

inhibitory factors including PD-1, Tim-3 on cell surface. FACS analysis revealed that both CD8+ T cells and CD4+ T cells have higher levels of PD-1 in COVID-19 infected patients, particularly in severe patients (20). As SARS-CoV-2 virus inactivates the anti-viral response at incipient stage, at the same time up regulation of NKG2A occurs and exhausted CD8+ and NK cells are created. Apart from improved expression of TIGIT, Tim-3, and PD-1 in CD8+ T cells, the impaired function of CD4+ T cells may worsen the disease and have made the patients with COVID-19 infection face to severe conditions.

Underlying causes of Lymphocytopenia in COVID-19 patients

Hypercytokinemia is a common feature noted in the severe covid-19 patients and it results from an excessive synthesis of pro-inflammatory cytokines in response to infection. Signs and symptoms of hypercytokinemia includes muscle pain, headache, hypotension, vasodilation, diarrhea and nausea. The presence of hypercytokinemia and lymphocytopenia in severe Covid-19 patients play a major role in the pathological process of COVID-19 and represents the lack of control of pathogens (21). It exacerbates inflammatory lesions in the target tissues, promotes massive T cell apoptosis and causes immune deficiency.

Another important factor that may be responsible for lymphocytopenia in COVID-19 patients is the host factor. It has been noted that compared to the mild and moderate COVID-19 patients, the severe COVID-19 patients are older and have comorbidities like hypertension, diabetes, cardiovascular and cerebrovascular diseases. Both age and chronic diseases causes persistent endothelial dysfunction resulting in dismantling of the cell junction, apoptosis of endothelial cell, disruption of the blood tissue barrier as well as the intensified leukocyte adhesion and extravasation these features contribute to lymphocytopenia in severe COVID-19 patients. Therefore, the host factors may also contribute to induce lymphocytopenia following Covid-19 infection.(22)

COVID-19 disease mainly affects the respiratory system with less damage to other functions. Evidence shows that damage to the alveolar epithelial cells was the main factor of COVID-19 related Acute respiratory distress syndrome (ARDS) compared with endothelial cells damage. Acute respiratory distress syndrome (ARDS) is a life-threatening lung condition occurs as a result of acute systemic inflammatory response caused by diffuse alveolar damage (DAD) in the lung. ARDS is characterised as acute severe hypoxemic respiratory failure with bilateral infiltration on chest imaging. The severity of the SARS-CoV-2 infection progresses in three stages. The early stage is characterised by flu-like symptoms which can develop to viral pneumonia as the disease progresses. The second stage is characterized by diffuse alveolar damage (DAD) with permanent damage to capillary endothelial cell and alveoli epithelial cells followed by leakage of protein-rich fluid into the alveolar space ultimately leads to hyaline membrane formation, damage to alveolar capillary barrier and inflammatory cell infiltration into the intra-alveolar space. The late stage is characterised by fibroblast proliferation and pulmonary thrombosis. Cytokine storm one of the main features of ARDS resulting from high proinflammatory cytokine level have critical role in the development and progression of ARDS. Studies

suggest that the high proinflammatory cytokines also plays important role in the induction of lymphocytopenia(23). The whole pathological process from extensive synthesis of cytokines, excessive apoptosis of lymphocytes resulting in a

cytokine storm, ARDS, and multiorgan failure are critical factor associated with COVID-19 disease severity and mortality. (24)

Possible Therapeutic Strategies

Elucidating the mechanisms underlying immune abnormalities in COVID-19 patients is essential for guiding potential immunotherapeutic strategies. Evidence shows that the immune response and COVID-19 are closely associated therefore immune characteristics is a potential biomarkers expression for disease progression as well as suitable target for treatment of COVID-19. Currently several drugs are approved for the treatment of Covid-19 disease which can prove to be potentially useful to lessen the impact of Sar-cov-2 infection.

Table provide potential therapeutic strategies which are promising for COVID -19 disease:

Pathological condition	Therapeutic strategies and function	Agents
Hypercytokinemia	Blockade of IL-6 signalling to relieve inflammation	Tocilizumab, Sarilumab
	Janus kinase inhibition to decrease cytokine level	Baricitinib, fedratinib, and ruxolitinib
	Treg cell-based therapy for Anti-inflammation	Tregs
	MSC-based therapy to repairs pulmonary epithelial cell damage and anti-inflammation	Mesenchymal stem/stromal cells (MSCs)
	Anti-inflammatory agents to Inhibits virus replication and reduce cytokine storm	DHODH inhibitors (25)
T-cell and NK cell lymphopenia	Natural killer cell treatment agent	NOVO-NK(26)
	Immunomodulators	IL-1 receptor antagonist -Anakinra and Interferons (alfa-2a, 2b)
	T-cell/NK cells lymphopenia	cyclophosphamide followed by fludarabine (27)
Exhausted lymphocytes	Blocked of inhibitory receptors programmed cell death protein 1 [PD-1], cytotoxic T-lymphocyte-associated protein 4(CTLA-4), T-cell immunoglobulin mucin-3 [Tim-3],2B4, lymphocyte-activation gene 3(LAG-3) to rescue T cell exhaustion(28)	PD1/PD-L1 Inhibitors- nivolumab and pembrolizumab
Apoptosis of T and NK cells	Inhibition of programmed cell death protein 1 [PD-1], therapy with antioxidants, cell cycle inhibitors, GSK3β inhibitors, and STATINS (29)	<ul style="list-style-type: none"> ➤ PD1/PD-L1 Inhibitors- nivolumab and pembrolizumab ➤ Antioxidants-Resveratrol ➤ Cell cycle inhibitors- flavopiridol, roscovitine ➤ STATINS-simvastatin ➤ GSK3β inhibitors- rosiglitazone

Hypercytokinemia

Several factors are associated with elevated cytokine release and overactive inflammatory response. It has been hypothesized that targeting the IL-6receptor (IL-6R) signalling pathway, JAK signalling pathway, Treg cells, Mesenchymal stem/stromal cells (MSCs), may alter the course of Covid-19 disease. Food and Drug Administration (FDA) has approved anti-IL-6 receptor monoclonal antibodies (30), JAK inhibitors (31), dihydroorotate dehydrogenase (DHODH) inhibitors for the management of COVID-19 patients. Transplantation of MSCs and Treg may represent another effective method with anti-inflammatory effects that defend against cytokine storm, repair pulmonary epithelial cell damage, and promote alveolar fluid clearance (32,33) to decreased inflammatory T cells inflammatory cytokines.

T-cell and NK cell lymphopenia

It has been shown that SAR-cov-2 virus induce immune changes and cause uncontrolled inflammatory responses in severe and critical patients of COVID-19. In lymphopenia there is impaired T-cells and NK cells, increase in inflammatory cytokines including IL-1, IL-6, which indicates disease severity and prognosis of COVID-19 patients. The NK

cells are cytotoxic lymphocytes that play a crucial role in bridging innate and adaptive immune system activity. Novocellbio in south Korea has confirmed that NOVO-NK, an autologous natural killer cell treatment agent gave promising results against SAR-COV-2 infection. Use of immunomodulators to reduce severe systemic inflammation is an appealing therapeutic approach. Immunomodulators including Anakinra (a human interleukin-1 receptor antagonist protein) (34), pegylated IFN alfa-2a and 2b(35) used to stimulate antiviral responses and reported to mitigate the excessive inflammation in patients infected with SARS-CoV-2 infection.

Exhausted lymphocytes

T-cell response are induced following infection, changes occur in gene expression, including the upregulation of inhibitory receptors. T cells exhibit an 'exhausted' state in chronic infections due to persistent high viral antigen load and inhibitory checkpoint signalling pathways (PD-1 LAG-3, 2B4, TIM-3, CTLA-4) (28). These inhibitory receptors collectively operate to negatively regulate the functional and proliferative potential of the responding cells. Moreover, elevated exhaustion levels and reduced functional diversity of T cells may predict severe progression in COVID-19

patients. Blocking the inhibitory pathways especially PD-1 pathway promotes the proliferation of virus-specific T cells, improves their functionality, and reduces viral loads.(36). Researchers have proposed that T-cell exhaustion frequently occurs in suppressive tumor microenvironments(37)

Apoptosis of T cells and NK cells

Apoptosis is a main pathologic feature induced by coronavirus infection. Apoptosis represents an organized mechanism of cellular suicide key to removal of damaged cells from the body. SAR-CoV-2 use various cellular signalling pathways by evoking pro-apoptotic receptors as a means to induce cell death, and eventually persistence. T-cells undergo apoptosis through TNF-related apoptosis-inducing ligand (TRAIL) and tumor necrosis factor alpha (TNF- α) on the cells during chronic infection (38). The frequency of apoptotic cells was significantly higher in severe COVID-19 patients. SAR-COV-2 infection may contribute to apoptosis and growth inhibition of hematopoietic cells that can also decrease the generation and differentiation of T cells and other lymphocytes. Apoptosis inhibitors would be beneficial for the treatment of COVID-19 disease and a multiple therapy with antioxidants, cell cycle inhibitors, GSK3 β inhibitors, and STATINS represent a suitable strategy for delaying the progression of the disease. (39)

Conclusion

Overall, low lymphocyte count and increased cytokine level are associated with severity of COVID-19 disease. T-cell play important role in the initial immune response. T cell count especially CD8+ was found to be remarkably decreased in the sever cases of COVID-19. Hence, reduced T-cell function and lymphocytes during COVID-19 infection may lead to aggravated inflammatory response. Thus, Lymphocytopenia can be used as a predictor of severity of the disease and prognosis of COVID-19 patients. However, much is yet to be learned and further research is needed to better understand the disease.

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