Comparison of Immune Response and Immunobiology in COVID-19 (Coronavirus Disease 2019) Mild-Moderate Degree and Severe Degree

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1. Introduction
COVID-19 (Coronavirus Disease 2019) is a new type of disease caused by a virus from the coronavirus, namely the Severe Acute Respiratory Syndrome Coronavirus 2 or SARS-CoV-2.¹ ² COVID-19 can cause respiratory system disorders, ranging from mild symptoms such as flu to lung infections, such as pneumonia. Studies in 2020 demonstrated that SARS-CoV-2 not only activates an antiviral immune response but can also induce an uncontrolled inflammatory response characterized by the marked release of proinflammatory cytokines in patients with severe COVID-19, leading to lymphopenia, lymphocytic dysfunction. And granulocyte and monocyte abnormalities. The immune pattern of COVID-19 includes lymphopenia, lymphocyte activation and dysfunction, granulocyte and monocyte abnormalities, increased cytokine production, and increased antibodies. Lymphopenia is a major feature of patients with COVID-19, especially in severe cases. CD69, CD38, and CD44 were highly expressed on the patient’s CD4+ and CD8+ T cells, and virus-specific T cells from severe cases displayed a central memory phenotype with high levels of IFN-γ, TNF-α, and IL-2. However, lymphocyte dysfunction demonstrated phenotypic exhaustion with Programmed Cell Death Protein-1 (PD1), T Cell Immunoglobulin Domain and Mucin Domain-3 (TIM3), and increased subfamily Killer Cell Lectin-Like Receptor Subfamily C Member 2 (NKG2A). Neutrophil levels were significantly higher in severe patients, while the percentages of eosinophils, basophils, and monocytes were reduced. Increased
production of cytokines, particularly IL-1β, IL-6, and IL-10, is another major characteristic of severe COVID-19. The number of IgG cells also increased, and there was a higher total antibody titer in COVID-19 patients.3-4

**Immune response in COVID-19 with a mild-moderate clinical degree**

The immune response that occurs in patients with mild-to-moderate COVID-19 manifestations is illustrated in a case report in Australia. This patient had an increase in CD38+HLA-DR+ T cells (activated T cells), especially CD8+ T cells, on days 7-9. In addition, there was an increase in antibody-secreting cells (ASCs) and follicular helper T cells in the blood on day 7, three days before symptom resolution. A progressive increase in SARS-CoV-2 IgM/IgG was also found from day 7 to day 20. These immunological changes persisted for up to 7 days after symptoms resolved. There was also a decrease in CD16+CD14+ monocytes compared to healthy controls. Activated natural killer (NK) cells HLA-DR+CD56+ and monocyte chemoattractant protein-1 (MCP-1; CCL2) were also found to be decreased, but the number of cells was the same as that of healthy controls. In patients with mild COVID-19 manifestations, there was no increase in proinflammatory chemokines and cytokines, even when symptomatic.5-7

**Immune response in COVID-19 with a severe clinical degree**

The difference in immunological profiles between mild and severe cases of COVID-19 can be seen in a study in China. A 2020 study found lower lymphocyte counts, higher leukocyte and neutrophil-lymphocyte ratios, and lower percentages of monocytes, eosinophils, and basophils in severe cases of COVID-19. Proinflammatory cytokines such as TNF-α, IL-1, and IL-6 as well as IL-8, and infection markers such as procalcitonin, ferritin, and C-reactive protein were also found to be higher in severe clinical cases. T Helper, T suppressor, and T regulatory were found to be decreased in COVID-19 patients with lower numbers of T helper and T regulatory in severe cases. Another case report in a COVID-19 patient with ARDS also showed a decrease in T CD4+ and CD8+. Lymphocytes CD4+ and CD8+ lymphocytes were in a hyperactivated state which was characterized by a high proportion of the HLA-DR+CD38+ fraction. T lymphocytes CD8+ were found to contain high concentrations of cytotoxic granules (31.6% positive for perforin, 64.2% positive for granulysin, and 30.5% positive for granulysin and perforin). In addition, an increase in the concentration of proinflammatory Th17 CCR6+ was also found.8-10

ARDS is the leading cause of death in COVID-19 patients. The cause of ARDS in SARS-CoV-2 infection is a cytokine storm, which is an uncontrolled systemic inflammatory response due to the release of large amounts of proinflammatory cytokines (IFN-α, IFN-γ, IL-1β, IL-2, IL-6, IL-7, IL-10 IL-12, IL-18, IL-33, TNF-α, and TGFβ) And large amounts of chemokines (CCL2, CCL3, CCL5, CXCL8, CXCL9, and CXCL10). Granulocyte-colony stimulating factor, interferon-γ-inducible protein 10, monocyte chemoattractant protein 1, and macrophage inflammatory protein 1 alpha were also increased. This excessive immune response can cause lung damage and fibrosis, resulting in functional disability.11-13

When the immune system recognizes a viral antigen, antigen-presenting cells process the antigen and present it to natural killer T cells and CD8+ cytotoxic T cells via the major histocompatibility complex (MHC). This presentation activates both innate and adaptive immunity leading to the production of large amounts of proinflammatory cytokines and chemokines. In some patients, this activation becomes so massive that a cytokine storm develops, resulting in thrombotic tendencies and multi-organ failure, and ultimately death.14

**2. Conclusion**

Differences in immunological features between mild-moderate and severe COVID-19 were seen in the levels of immunological cells and inflammatory markers.
3. References