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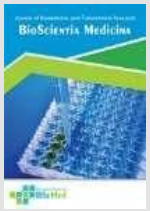

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Relationship between the Number of CD4+ and CD8+ Cells in Patients with COVID-19 (Coronavirus Disease 2019) at Dr. Mohammad Hoesin General Hospital, Palembang, Indonesia

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A B S T R A C T

Background: The pathogenesis of COVID-19 involves complex immunological processes that can predispose to disease severity. In COVID-19 patients, there will be changes in the number of CD4 + and CD8 + cells which are part of lymphocyte cells in the specific immune system. This study aims to see the relationship between CD4+ and CD8+ cell counts in COVID-19 patients at Dr. Mohammad Hoesin Hospital Palembang, Indonesia. **Methods:** This research is an observational study with a case series approach. A total of 30 study subjects who were COVID-19 patients participated in this study. The number of CD4+ and CD8+ cells was assessed, then correlation analysis was performed with the Spearman test, $p<0.05$. **Results:** The correlation between CD4+ and CD8+ has a value of $R = 0.875$ and $p<0.01$. This shows that CD4+ and CD8+ have a strong positive correlation and are statistically significant. **Conclusion:** The increase in the number of CD4+ cells will be followed by an increase in the number of CD8+ cells in COVID-19 patients at Dr. Mohammad Hoesin General Hospital Palembang, Indonesia.

1. Introduction

Coronavirus disease 2019 (COVID-19) was discovered at the end of 2019, precisely in December in Wuhan City, Hubei Province, China, and then spread to almost all over the world. COVID-19 is caused by a new type of beta coronavirus that tends to be similar to SARS-CoV and MERS-CoV. As of June 26th, 2021, data from WHO for confirmed cases of COVID-19 in the world there are > 179 million cases with a death rate of nearly four million cases. In Indonesia there are 2,093,962 confirmed cases with a death rate of 56,729 (case fatality rate / CFR 2.7%). In South Sumatra, confirmed cases as of June 26th, 2021, there were around 27,370 cases with 1386 people who died (CFR 5.06%). For the Palembang city area, there were 15,029 confirmed people with a death rate of 654 people (CFR 4.35%). From this data, we can see that the case fatality rate in South Sumatra, especially the city of Palembang, has exceeded the world and national CFR.[1-5]

In COVID-19 patients, there will be changes in the number of CD4+ and CD8+ cells, which are part of the lymphocyte cells in the specific immune system. In the

specific immune system, there is cellular immunity in the form of T cells that help B cells produce antibodies, initiate and increase inflammation through inflammatory mediators, and lyse antigen target cells. In contrast to B cells, T cells consist of several subsets with different functions, namely Th1, Th2, Tdth, CTL or Tc cells, Ts or Tr or Th3 cells. The main function of the cellular immune system is to defend against intracellular bacteria, viruses, fungi, parasites, and malignancies. If the virus infects the cells will experience changes, both in form and number. Cells that play a role in cellular immunity are CD4+ cells that activate Th1 cells, which then activate macrophages to destroy microbes, and CD8+ cells that destroy infected cells.[6]

Viral and host factors play a role in SARS-CoV-2 infection. The cytopathic effect of the virus and its ability to overpower the immune response determines the severity of the infection. Dysregulation of the immune system then plays a role in tissue damage in SARS-CoV-2 infection. Inadequate immune response leads to viral replication and tissue damage. On the other hand, an exaggerated immune response can lead to tissue damage. The emergence of adaptive immunity in response to SARS-CoV-2 infection occurs within the first 7 to 10 days of infection. Strong B-cell memory and plasma blast expansion are detected early in infection with the secretion of serum IgM on days 5 to 7 and IgG on days 7 to 10. SARS-CoV-2 also activates T lymphocytes in the first week of infection. Memory CD4+ cells are specific. Virus and CD8+ T cells were reported to peak in the second week of infection. The difference in immunological profiles between mild and severe COVID-19 cases can be seen in several studies in China that found lower lymphocyte counts, leukocytes, and higher neutrophil-lymphocyte ratios, as well as lower monocyte, eosinophil, and basophil percentages in COVID-19 cases. - 19 heavy ones. Pro-inflammatory cytokines such as TNF-α, -, IL-1, and IL-6, as well as IL-8 and infection markers such as procalcitonin, ferritin, and CRP, were found to be higher in severe clinical cases. Helper T cells, suppressor T cells, and regulatory T cells were found to be decreased in COVID-19 patients with lower numbers of helper and regulatory T cells in severe cases.[7,8]

In positive confirmed COVID-19 patients with severe clinical symptoms, the immunological profile results are different from those of mild clinical. Based on Huang et al.'s 2020 meta-analysis, T cells, CD8+ T cells, B cells, NK cells, and total lymphocyte cell counts all showed statistically significant reductions in patients with severe/critical COVID-19 disease compared with mild/moderate disease. So it can be concluded that this parameter is good for screening, diagnostic support, and monitoring of the severity of the disease. The morbidity and mortality of COVID-19 disease can be caused by direct damage to the host by the pathogen or additional damage to host tissues by an exaggerated immune response to the pathogen. According to Jiang et al.'s 2020 study, a progressive decrease in peripheral lymphocytes is one of the clinical warning indicators for severe and critical cases in adults, and many studies have also reported lymphopenia, especially for CD8+ T cell reduction in COVID-19 patients. The results of Jiang's study showed a decrease in total lymphocytes, CD8+ T cells, and NK cells in COVID-19 patients compared to healthy controls, but there was no significant decrease for CD4+ T cells in COVID-19 patients compared to healthy controls. However, in the study of Ganji Ali et al. in 2020, it was found that the expression of CD8+ in CTL had a significant increase in the patient group compared to the healthy control group. So from this study, it is said that the immune response to COVID-19 infection occurs through the overexpression of CD8+ and hyperactivity of the CTL antiviral response. However, there was no change in the ratio and the number of CD4+ and CD8+ cells. [10,11,12] This study aims to see the relationship between the number of CD4+ and CD8+ cells in COVID 19 patients at Dr. Mohammad Hoesin General Hospital Palembang, Indonesia. This study is one of the initial studies that aim to explore the relationship between CD4+ and CD8+ in COVID-19 patients.

2. Methods

This study is an analytical observational study with a case series approach to assessing the relationship between CD4+ and CD8+ cell counts in hospitalized COVID-19 patients in Dr. Mohammad Hoesin General Hospital, Palembang, Indonesia. A total of 30 research subjects took part in this study, where research subjects met the inclusion criteria, namely patients with confirmed cases of COVID-19 from the SARS-CoV-2 RT-PCR test who were hospitalized in March - May 2021, aged more than 17 years and agreed to participate in this study. This study has been approved by the health and research ethics commission of Dr. Mohammad Hoesin General Hospital, Palembang (No. 45/kepkrsmh/2022). The number of CD4+ and CD8+ T cells was measured on the first day of confirmation in the isolation ward and on the 10th day after the onset of COVID-19 symptoms. The examination uses the flow cytometry method, which is carried out in an accredited laboratory. The unit value used is cells/mm^3 (cells per cubic millimeter).

Data analysis was carried out with the help of SPSS Version 25 software. Univariate analysis was performed to present descriptive data and tabulated data. Then proceed with bivariate analysis with the Spearman correlation test so that the R-value and p-value will be obtained. A positive R-value indicates that an increase in the number of CD4+ cells is in line with an increase in the number of CD8+ cells. At the same time, the negative R-value indicates that the increase in the number of CD4+ cells is inversely proportional to the CD8+ value. The closer the R-value to 1, the stronger the correlation between CD4+ and CD8+. The p-value is set at 5% or 0.05, where if the p-value <0.05 indicates a significant relationship between CD4+ and CD8+.

3. Results

Table 1 shows the sociodemographic as well as clinical study subjects. The majority of research subjects are productive age, male gender, and high school education. All study subjects had comorbidities, most of which were comorbid with hypertension and diabetes mellitus. More than 25% of the study subjects had received vaccinations, and the majority had normal body mass index.

Table 1. Baseline characteristics of research subjects

Characteristics	Research subjects (n=30)
Age	51.39+12.15
18-60 years	17 (56.7%)
≥60 years	13 (43.3%)
Gender	
Male	18 (60.0%)
Female	12 (40.0%)
Education	
Elementary	4 (13.3%)
Junior	5 (16.7%)
High School	17 (56.7%)
Bachelor	4 (13.3%)
Occupation	
Not working	2 (6.7%)
Labor	5(16.6%)
Farmer	2(6.7%)
Civil Servant	4(13.3%)
Private employee	17(56.7%)
Comorbid	
Diabetes Mellitus	12 (40, 0%)
Hypertension	14 (46.7%)
Chronic Kidney Disease	4 (13.3%)
Body Mass Index	
<18.5	3 (10.0%)
18.5 – 25	20 (66.7%)
25.1 – 27	7 (23.3%)
Vaccination	8 (26.7%)
The onset of symptoms (days)	5 (1-7)
Interval (days)	5 (3-9)
Oxygen Sat (%)	94 (82-99)
Outcome	
Died	7 (23.3%)

Table 2. Relationship between CD4+ and CD8+ cell counts

Relationship	Cell count CD8+	
Cell counts CD4+	r=0.875	P=<0.01

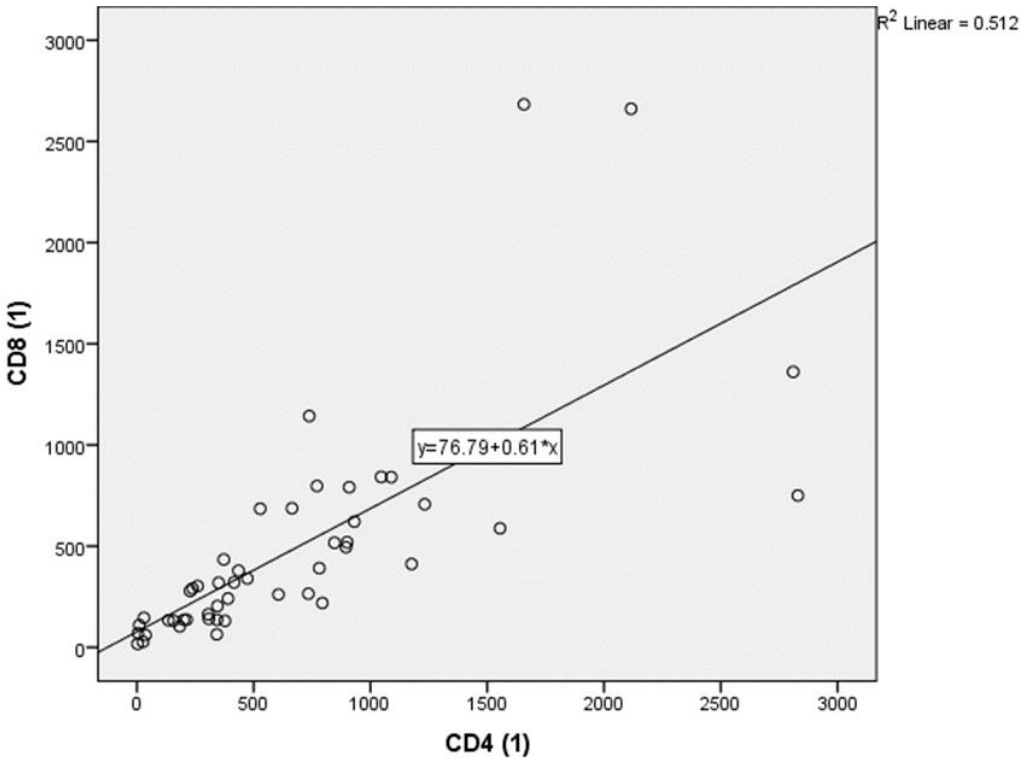

Figure 1. The relationship between the number of CD4+ and CD8+ cells

Table 2 shows that the R-value is 0.875, which indicates that the R-value is positive. This indicates that the higher the number of CD4+ cells will be followed by an increase in the number of CD8+ cells. An R-value close to 1 indicates that the correlation between CD4+ and CD8+ is strong. The p-value showed <0.01, indicating that the correlation between CD4+ and CD8+ was statistically significant.

4. Discussion

Lymphopenia and drastic reductions in CD4+ T cell counts in COVID-19 patients have been associated with poor clinical outcomes.[13] Because CD4+ T cells play an important role in regulating the response to viral infection by comparing the T cell response in COVID-19. CD4+ T-helper cells are important in mediating protective humoral immunity by stimulating B cells to produce virus-specific antibodies. On the other hand, CD8+ T cells are responsible for the elimination of infected cells, mainly through the production of lysozyme and pro-inflammatory cytokines, and have an important role in controlling various types of viruses through the secretion of cytokines. CD4+ and CD8+ T cell counts are reduced in COVID-19 and are associated with poor clinical outcomes.[14-17] Another study stated that decreased CD4+ and CD8+ cell levels were common in patients with COVID-19, and there was no significant difference in decreased CD4+ cell levels between patients with moderate and severe COVID-19, while patients with severe COVID-19 were more likely to have decreased CD4+ cell levels, suggesting that decreased CD4+ cell levels may reflect disease severity.[18-20]

CD4+ cells can influence the differentiation and maturation of other cells by producing cytokines and chemokines, and interferon-γ secretion is a cytokine with antiviral and immune activity. Patients infected with SARS-CoV-2 exhibit Th1 cell responses and use cellular immunity to control infection. Viral infection causes a complete change in cellular immunity, which is manifested by a decrease in lymphocytes, a change in the distribution of the T cell subset, and an increase in the concentration of cytokines. But the mechanism of SARS-CoV-2 infection that causes a decrease in lymphocytes and lymphocyte subsets is still unclear. Increased concentrations of IL-10, IL-6, and TNF-α have been reported to be negatively associated with total T cell levels, CD4+ cell levels, and CD8+ cell levels.[21-24] Theoretically, the first week is the virulence phase, where CD8+ cells as cytotoxic T cells will be deployed to infected cells so that a more massive proliferation of CD8+ is needed. For this reason, the body will stimulate CD4+ to increase its activity in order to support CD8+ proliferation. However, as a result, powerful pro-inflammatory cytokines will also be formed, including TNF-α and IL-6, which ultimately trigger a cytokine storm. By that time, early in the second week of onset, CD4+ had started to decline due to feedback from cytokine storm conditions. On the other hand, CD8+ is still trying to increase its proliferation, so it still shows an increase in its number in the blood at the beginning of the second week. But then there will be 'exhausted', especially in patients who have entered a severe and critical condition, then, in the end, the number of CD8+ cells will decrease.[25-27]

5. Conclusion

There is a strong and significant positive relationship between the number of CD4+ cells and the number of CD8+ cells in COVID 19 patients at Dr. Mohammad Hoesin General Hospital Palembang, Indonesia.

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