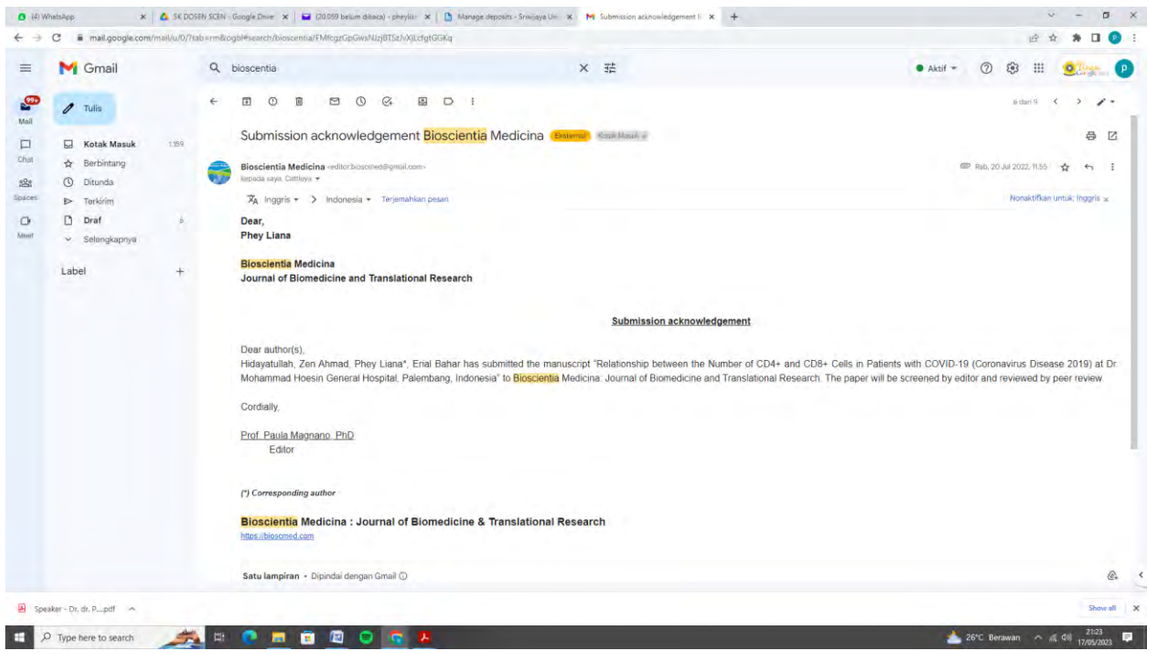

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Submission acknowledgement

Dear author(s),
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(*) Corresponding author

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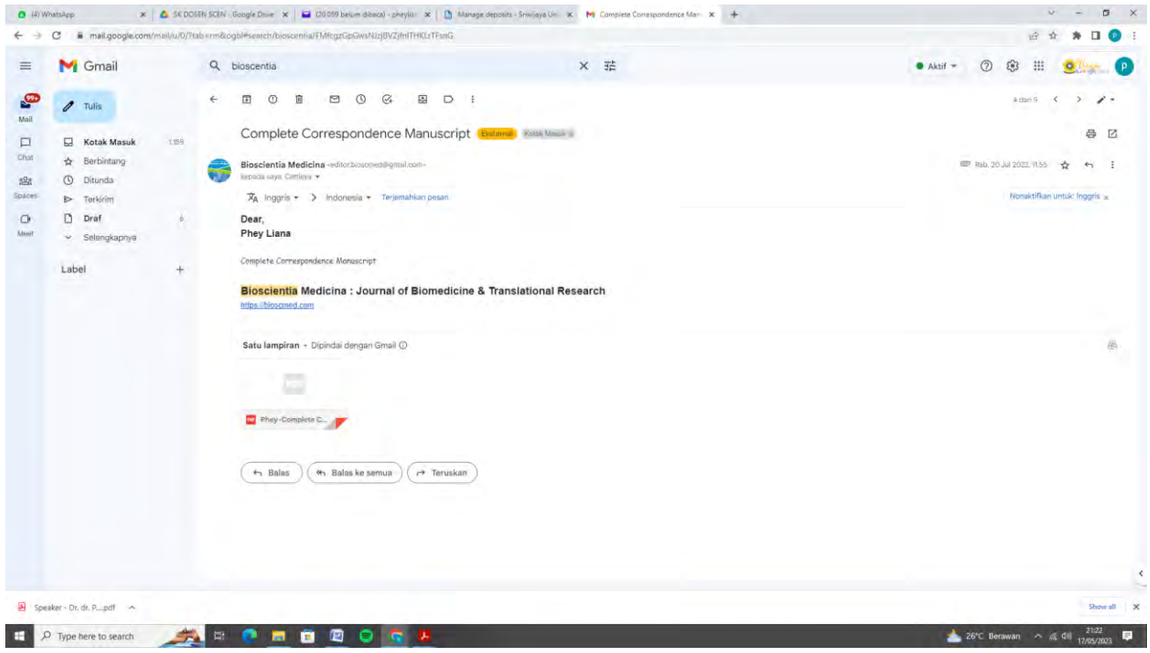

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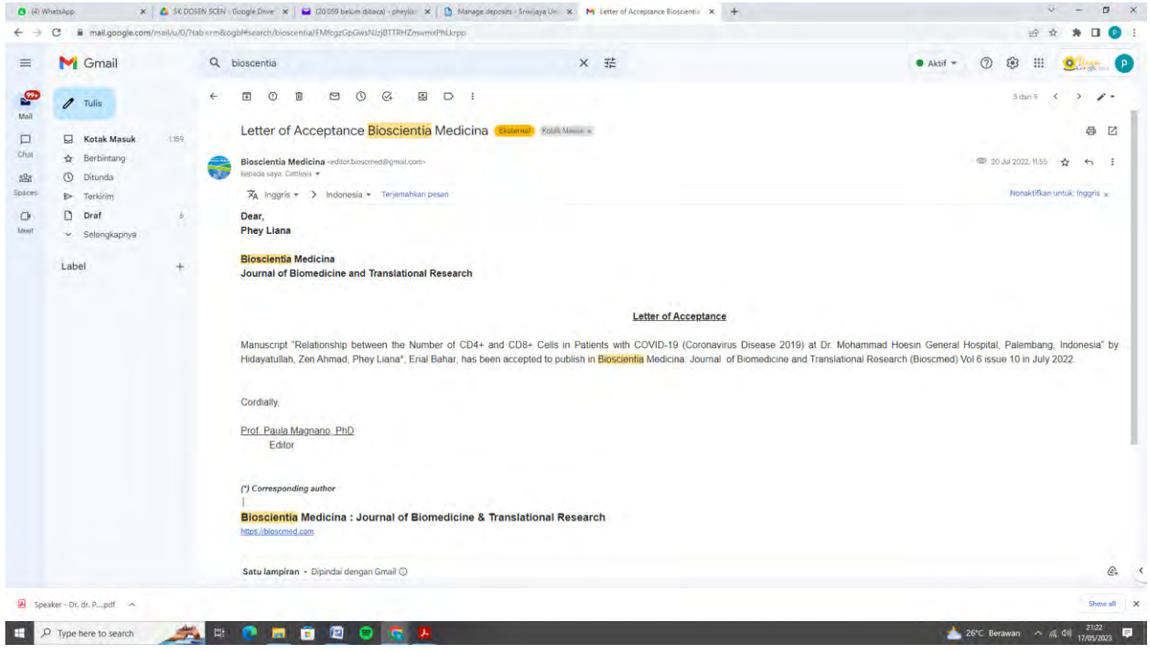

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Dear,
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Bioscientia Medicina
Journal of Biomedicine and Translational Research

Letter of Acceptance

Manuscript "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" by Hidayatullah, Zen Ahmad, Phey Liana*, Erial Bahar, has been accepted to publish in Bioscientia Medicina: Journal of Biomedicine and Translational Research (Bioscmed) Vol 6 issue 10 in July 2022.

Cordially,

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Editor

(*) Corresponding author

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Editor HM Publisher

(*) Corresponding author

Tittle of Manuscript: **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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Certificate Service Confirmation

To whom it may concern,
HM Publisher provided comprehensive editing services for manuscript entitled 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. The edit has achieved Grade A: priority publishing; no language polishing required after editing. Should you require any additional information, please do not hesitate to contact me.

Regards,

Khrishna Murti, PhD
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Submitted to the journal "Bioscientia Medicina: Journal of Biomedicine and Translational Research (June 24th, 2022)

The Relationship between CD4+ and CD8+ Cell Counts in COVID 19 (Coronavirus Disease 2019) Patients at RSUP Dr. Moh Hoesin Palembang Indonesia

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Abstract

Background. The pathogenesis of Covid-19 involves complex immunological processes that can predispose to the severity of the disease. In COVID19 patients, there will be a change in the number of CD4+ and CD8+ cells that 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 RSUP Dr Moh Hoesin Palembang Indonesia. **Methods.** This study is an observational study with a case series approach. A total of 30 study subjects who were COVID 19 patients took part in the study. An assessment of the number of CD4 + and CD8 + cells was carried out, then a correlation analysis was carried out with the spearman test, $p<0.05$. **Results.** The correlation between CD4+ and CD8+ has the value $R = 0.875$ and $p<0.01$. This suggests that CD4+ and CD8+ are strongly correlated positively and statistically meaningful. **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. Moh Hospital. Hoesin Palembang Indonesia.

Keywords: COVID 19; CD4+; CD8+; Pathogenesis

1.Introduction

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

In COVID19 patients, there will be a change in the number of CD4+ and CD8+ cells that 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. Unlike 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. If the virus infects, the cell will undergo changes, both in shape and number. Cells that play a role in cellular immunity are CD4+ cells that activate Th1 cells which further activate macrophages to destroy microbes and CD8+ cells that destroy infected cells. [6th]

Viral factors and cultists have a role in SARS-CoV-2 infection. The cytopathic effects of the virus and its ability to defeat the immune response determine the severity of the infection. Dysregulation of the immune system then plays a role in tissue damage in SARS-CoV-2 infection. An inadequate immune response leads to viral replication and tissue damage. On the other hand, an excessive immune response can lead to tissue damage. The appearance of adaptive immunity in response to infection with SARS-CoV-2, occurs in the first 7 to 10 days of infection. Strong B cell memory and plasmablast expansion were detected at the beginning of infection with serum IgM secretion on days 5 to 7 and IgG on days 7 to 10. SARS-CoV-2 also activates lymphocyte T cells in the first week of infection, virus-specific memory CD4+ cells and CD8+ T cells reportedly peaked in the second week of infection. Differences in immunological profiles between mild and severe COVID-19 cases can be seen from several studies in China that have obtained lower lymphocyte counts, leukocytes and a higher neutrophil-lymphocyte ratio, as well as a lower

percentage of monocytes, eosinophils, and basophils in severe COVID-19 cases. Pro-inflammatory cytokines namely TNF-α, IL-1 and IL-6 as well as IL-8 and infection markers such as procalcitonin, ferritin and CRP were obtained higher in cases with severe clinical. Helper T cells, rectifier T, and regulatorY T were found to decrease in COVID-19 patients with lower numbers of helper and regulatorY T cells in severe cases. [7.8]

In covid-19 positive confirmed patients with severe clinical symptoms gave the results of an immunological profile that was different from 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 a statistically significant decrease in patients with severe/critical COVID-19 disease compared to mild/moderate illness. So it can be concluded that this parameter is good for screening, diagnostic support, and monitoring the severity of the disease. The morbidity and mortality of the COVID-19 disease can be caused by direct damage to the host by the pathogen or additional damage to the host tissue by an excessive immune response to the pathogen. According to a 2020 study by Jiang et al that the 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 lymphophenia especially for the reduction of CD8+ T cells 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 the healthy control group, but there was no significant decrease in CD4+ T cells in COVID-19 patients compared to healthy controls. However, in the 2020 study of Ganji Ali et al. in 2020, the expression of CD8+ in CTL experienced a significant increase in the patient group compared to the healthy control group. So from the study, it is said that the immune response to COVID 19 infection occurs through excessive expression of CD8+ and hyperactivity of the CTL antiviral response. However, there was no change in the ratio and number of cells of CD4+ and CD8+. [10,11,12] This study aims to see the relationship between CD4+ and CD8+ cell counts in COVID 19 patients at RSUP Dr Moh Hoesin Palembang Indonesia. This study is one of the initial studies that aims to explore the link between CD4+ and CD8+ in COVID 19 patients.

2.Methods

This study is an analytical observational study with a case series approach to assess the relationship between CD4+ and CD8+ cell counts in COVID 19 inpatients at Dr. Moh Hoesin Hospital Palembang Indonesia. A total of 30 study subjects participated in this study, where the

study subjects met the inclusion criteria, namely patients with confirmed cases of COVID-19 from the SARS-CoV-2 RT-PCR test examination were hospitalized in March - May 2021, aged more than 17 years and agreed to participate in this study. This study has received approval from the Research and Health Ethics Commission of RSUP Dr. Moh Hoesin Palembang (No. 45/kepkrsmh/2022). The number of CD4+ and CD8+ T cells was measured on the first day of confirmation in the isolation inpatient room and the 10th day after covid-19 symptoms emerged. The examination uses the flow cytometry method which is carried out in an accredited laboratory. The unit value used is cell / mm^3 (cells per cubic millimeter).

Data analysis was carried out with the help of SPSS Version 25 software. Univariate analysis is performed to present descriptive data and tabulate data. Then continued the bivariate analysis with a spearman correlation test so that R and p values 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. While the negative R value indicates that the increase in the number of CD4+ cells is inversely proportional to the CD8+ value. The more the R value approaches the value of 1 indicates the stronger the correlation between CD4+ and CD8+. The P value is set at 5% or 0.05, where if the p value of the < 0.05 indicates a meaningful relationship between CD4+ and CD8+.

3. Results

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

Table 1. Baseline Characteristics of Research Subjects

Characteristic	Research Subjects (n=30)
Age (Years)	51.39±12.15
18-60 years	17 (56,7%)

≥60 years	13 (43,3%)
Gender	
Man	18 (60,0%)
Woman	12 (40,0%)
Education	
SDSMP	4 (13,3%)
SMA	5 (16,7%)
Bachelor	17 (56,7%)
	4 (13,3%)
Work	
Doesn't work	
Laborer	2 (6,7%)
Farmer	5(16,6%)
Civil servants	2(6,7%)
Private employees	4(13,3%)
	17(56,7%)
Comorbidities	
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%)
Onset of Symptoms (days)	5 (1-7)
Difference Between (days)	5 (3-9)
Sat Oxygen (%)	94 (82-99)
External	
Die	7 (23,3%)

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

Relationship	Cd8+ Cell Count	
Cd4+ Cell Count	r=0.875	P=<0.01

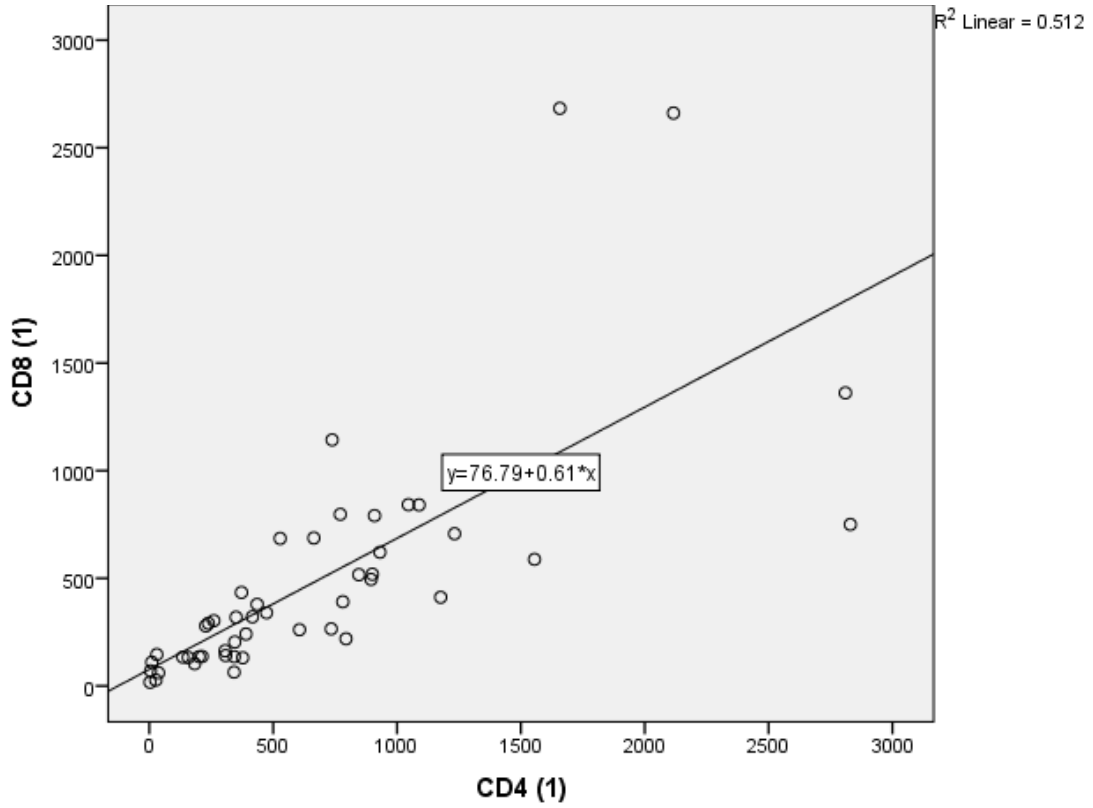

Figure 1. Relationship between CD4+ and CD8+ Cell Count

Table 2 shows that the value of R is 0.875 which indicates that the value of R is positive. This suggests 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. A p value of <0.01 indicates that the correlation between CD4+ and CD8+ is statistically meaningful.

4. Discussion

Lymphopenia and a drastic decrease in cd4+ T cell count in COVID-19 patients have been linked to poor clinical outcomes. [13] Because CD4+ T cells play an important role in regulating the response to viral infections by comparing the response of T cells 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 cytosomes, and have an important role in controlling different 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 the decrease in CD4+ cell levels between patients with moderate and severe COVID-19, while patients with severe COVID-19 were more likely to experience a decrease in CD4+ cell levels, suggesting that a decrease in CD4+ cell levels could reflect the severity of the disease. [18-20]

CD4+ cells can influence the differentiation and maturation of other cells by producing cytokines and chemokines, and interferon-γ secretions are cytokines with antiviral and immune activity. Patients infected with SARS-CoV-2 showed a Th1 cell response and used cellular immunity to control the infection. Viral infections cause a thorough change in cellular immunity, which is manifested by a decrease in lymphocytes, a change in the distribution of a subset of T cells and an increase in the concentration of cytokines. But the mechanism of infection with SARS-CoV-2 that causes a decrease in lymphocytes and a subset of lymphocytes remains 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] In theory, in the first week, it is the virulence phase where CD8+ cells as cytotoxic T cells will be parachuted into infected cells so that a more massive proliferation of CD8+ is needed. For this reason, the body will spur CD4 + to increase its activity in order to support the proliferation of CD8 +. However, as a result, great pro-inflammatory cytokines will also be formed, including TNF–α and IL-6 which ultimately spurred a cytokine storm. At the beginning of the second week of receipts, CD4+ had already begun to decline due to feedback from cytokine storm conditions. On the other hand, CD8+ is still trying to increase its proliferation so that it still shows an increase in its amount in the blood at the beginning of week two. But then there will be '*exhausted*' events, especially in patients who have entered a severe and critical state, then in the end the number of CD8 + cells will decrease. [25-27]

5. Conclusion

There is a strong and meaningful positive correlation between the number of CD4+ cells and the number of CD8+ cells in COVID 19 patients at Dr. Moh Hoesin Hospital Palembang Indonesia.

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Submitted to the journal “Bioscientia Medicina: Journal of Biomedicine and Translational Research (June 24th, 2022)

Bioscientia Medicina

Journal of Biomedicine and Translational Research

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Submission acknowledgement

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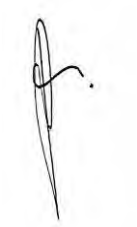

Prof. Paula Magnano, PhD

Editor HM Publisher

(*) Corresponding author

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Peer Review Results

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Prof. Paula Magnano, PhD
Editor HM Publisher

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Reviewer 1

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Abstract →3

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Keywords: COVID 19; CD4+; CD8+; Pathogenesis →2

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

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Viral factors and cultists have a role in SARS-CoV-2 infection. The cytopathic effects of the virus and its ability to defeat the immune response determine the severity of the infection. Dysregulation of the immune system then plays a role in tissue damage in SARS-CoV-2 infection. An inadequate immune response leads to viral replication and tissue damage. On the other hand, an excessive immune response can lead to tissue damage. The appearance of adaptive immunity in response to infection with SARS-CoV-2, occurs in the first 7 to 10 days of infection. Strong B cell memory and plasmablast expansion were detected at the beginning of infection with serum IgM secretion on days 5 to 7 and IgG on days 7 to 10. SARS-CoV-2 also activates lymphocyte T cells in the first week of infection, virus-specific memory CD4+ cells and CD8+ T cells reportedly peaked in the second week of infection. Differences in immunological profiles between mild and severe COVID-19 cases can be seen from several studies in China that have obtained lower lymphocyte counts, leukocytes and a higher neutrophil-lymphocyte ratio, as well as a lower

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In covid-19 positive confirmed patients with severe clinical symptoms gave the results of an immunological profile that was different from 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 a statistically significant decrease in patients with severe/critical COVID-19 disease compared to mild/moderate illness. So it can be concluded that this parameter is good for screening, diagnostic support, and monitoring the severity of the disease. The morbidity and mortality of the COVID-19 disease can be caused by direct damage to the host by the pathogen or additional damage to the host tissue by an excessive immune response to the pathogen. According to a 2020 study by Jiang et al that the 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 lymphophenia especially for the reduction of CD8+ T cells 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 the healthy control group, but there was no significant decrease in CD4+ T cells in COVID-19 patients compared to healthy controls. However, in the 2020 study of Ganji Ali et al. in 2020, the expression of CD8+ in CTL experienced a significant increase in the patient group compared to the healthy control group. So from the study, it is said that the immune response to COVID 19 infection occurs through excessive expression of CD8+ and hyperactivity of the CTL antiviral response. However, there was no change in the ratio and number of cells of CD4+ and CD8+. [10,11,12] This study aims to see the relationship between CD4+ and CD8+ cell counts in COVID 19 patients at RSUP Dr Moh Hoesin Palembang Indonesia. This study is one of the initial studies that aims to explore the link between CD4+ and CD8+ in COVID 19 patients.

2.Methods →5

This study is an analytical observational study with a case series approach to assess the relationship between CD4+ and CD8+ cell counts in COVID 19 inpatients at Dr. Moh Hoesin Hospital Palembang Indonesia. A total of 30 study subjects participated in this study, where the

study subjects met the inclusion criteria, namely patients with confirmed cases of COVID-19 from the SARS-CoV-2 RT-PCR test examination were hospitalized in March - May 2021, aged more than 17 years and agreed to participate in this study. This study has received approval from the Research and Health Ethics Commission of RSUP Dr. Moh Hoesin Palembang (No. 45/kepkrsmh/2022). The number of CD4+ and CD8+ T cells was measured on the first day of confirmation in the isolation inpatient room and the 10th day after covid-19 symptoms emerged. The examination uses the flow cytometry method which is carried out in an accredited laboratory. The unit value used is cell / mm^3 (cells per cubic millimeter).

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

Relationship	Cd8+ Cell Count	
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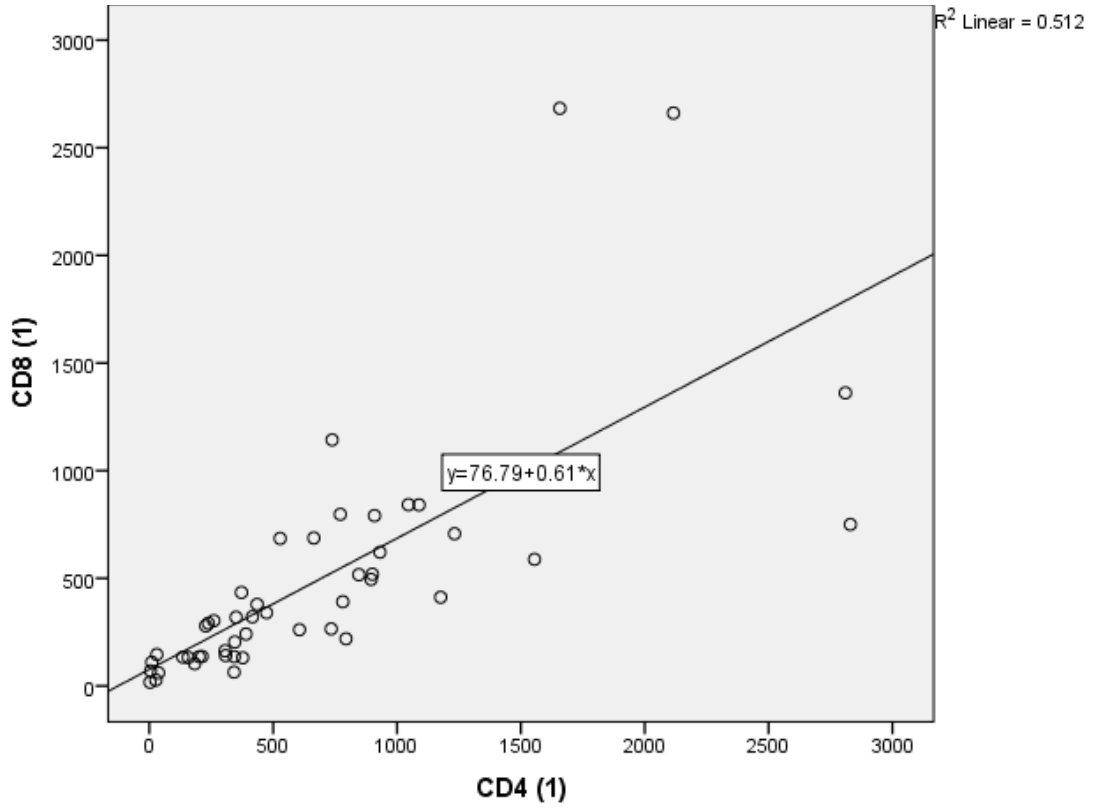

Figure 1. Relationship between CD4+ and CD8+ Cell Count

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4. Discussion →7

Lymphopenia and a drastic decrease in cd4+ T cell count in COVID-19 patients have been linked to poor clinical outcomes. [13] Because CD4+ T cells play an important role in regulating the response to viral infections by comparing the response of T cells 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 cytosomes, and have an important role in controlling different 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 the decrease in CD4+ cell levels between patients with moderate and severe COVID-19, while patients with severe COVID-19 were more likely to experience a decrease in CD4+ cell levels, suggesting that a decrease in CD4+ cell levels could reflect the severity of the disease. [18-20]

CD4+ cells can influence the differentiation and maturation of other cells by producing cytokines and chemokines, and interferon-γ secretions are cytokines with antiviral and immune activity. Patients infected with SARS-CoV-2 showed a Th1 cell response and used cellular immunity to control the infection. Viral infections cause a thorough change in cellular immunity, which is manifested by a decrease in lymphocytes, a change in the distribution of a subset of T cells and an increase in the concentration of cytokines. But the mechanism of infection with SARS-CoV-2 that causes a decrease in lymphocytes and a subset of lymphocytes remains 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] In theory, in the first week, it is the virulence phase where CD8+ cells as cytotoxic T cells will be parachuted into infected cells so that a more massive proliferation of CD8+ is needed. For this reason, the body will spur CD4 + to increase its activity in order to support the proliferation of CD8 +. However, as a result, great pro-inflammatory cytokines will also be formed, including TNF–α and IL-6 which ultimately spurred a cytokine storm. At the beginning of the second week of receipts, CD4+ had already begun to decline due to feedback from cytokine storm conditions. On the other hand, CD8+ is still trying to increase its proliferation so that it still shows an increase in its amount in the blood at the beginning of week two. But then there will be '*exhausted*' events, especially in patients who have entered a severe and critical state, then in the end the number of CD8 + cells will decrease. [25-27]

5. Conclusion →8

There is a strong and meaningful positive correlation between the number of CD4+ cells and the number of CD8+ cells in COVID 19 patients at Dr. Moh Hoesin Hospital Palembang Indonesia.

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Reviewer Comment:

1→ Title of Manuscripts should be explained independent variable and dependent variable also subject of study.

2→ Keywords should be showed the main words of the study, the authors can use MeSH to develop keywords.

3→ Abstract should be showed the main of background, methods, results and conclusion of study.

- Background abstract should be showed the urgency of study and why the study important, in simple way.
- Conclusion should be wrote in simple way, specific to the main results. Conclusion in abstract should not showed statistic results.

4→Introduction should be showed the urgency of study (epidemiology data), biological plausibility concept, and lack of knowledge in the study.

- Paragraph 1→ need improvement in urgency of study and explain more about epidemiology data. Authors do not only show the data, but try to elaborate and make

comparison about the data from year to year.

- Paragraph 2 and 3 need improvement to focus in biological plausibility concept.

5→ Methods should be showed more about how the study develop. Methods should be showed the design of study; population, sample and sample size of study; inclusion criteria; place of study; ethical clearence steatment; independent and dependent variable; data analysis.

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6→ Results should be showed baseline characteristics subject of study, main results of study. Authors must be focused and try to make results no more table and figure.

7→ Discussion should be explored more biological plausibility, not only showed about statistical results.

8→ Conclusion should more specific and not more showed statistical results

9→ Authors must check the references for make update references. References should no more than 10 years.

Reviewer 2

The Relationship between CD4+ and CD8+ Cell Counts in COVID 19 (Coronavirus Disease 2019) Patients at RSUP Dr. Moh Hoesin Palembang Indonesia → Check title

Hidayatullah[1], Zen Ahmad[1], Phey Liana[2*], Erial Bahar[3]

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[2]Department of Clinical Pathology, Faculty of Medicine, Universitas Sriwijaya/ Dr. Mohammad Hoesin General Hospital, Palembang, Indonesia

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Abstract →1

Background. The pathogenesis of Covid-19 involves complex immunological processes that can predispose to the severity of the disease. In COVID19 patients, there will be a change in the number of CD4+ and CD8+ cells that 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 RSUP Dr Moh Hoesin Palembang Indonesia. **Methods.** This study is an observational study with a case series approach. A total of 30 study subjects who were COVID 19 patients took part in the study. An assessment of the number of CD4 + and CD8 + cells was carried out, then a correlation analysis was carried out with the spearman test, $p<0.05$. **Results.** The correlation between CD4+ and CD8+ has the value $R = 0.875$ and $p<0.01$. This suggests that CD4+ and CD8+ are strongly correlated positively and statistically meaningful. **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. Moh Hospital. Hoesin Palembang Indonesia.

Keywords: COVID 19; CD4+; CD8+; Pathogenesis

1.Introduction →2

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

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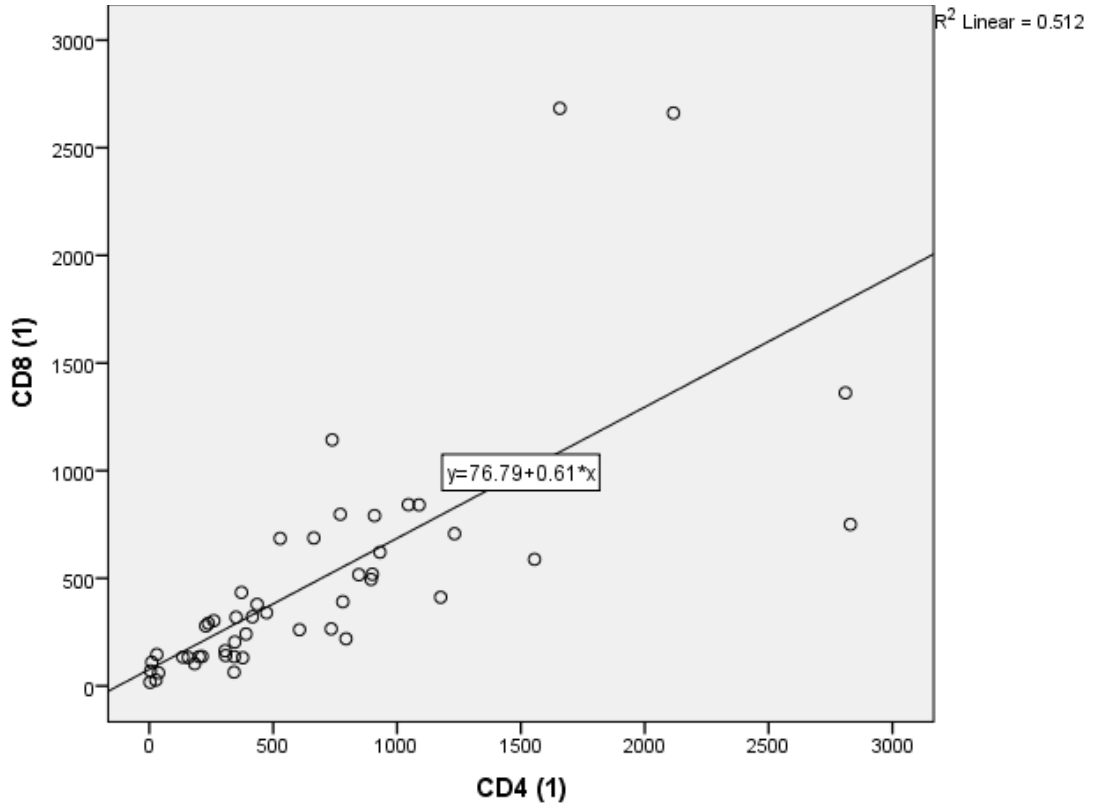

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Lymphopenia and a drastic decrease in cd4+ T cell count in COVID-19 patients have been linked to poor clinical outcomes. [13] Because CD4+ T cells play an important role in regulating the response to viral infections by comparing the response of T cells 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 cytosomes, and have an important role in controlling different 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 the decrease in CD4+ cell levels between patients with moderate and severe COVID-19, while patients with severe COVID-19 were more likely to experience a decrease in CD4+ cell levels, suggesting that a decrease in CD4+ cell levels could reflect the severity of the disease. [18-20]

CD4+ cells can influence the differentiation and maturation of other cells by producing cytokines and chemokines, and interferon-γ secretions are cytokines with antiviral and immune activity. Patients infected with SARS-CoV-2 showed a Th1 cell response and used cellular immunity to control the infection. Viral infections cause a thorough change in cellular immunity, which is manifested by a decrease in lymphocytes, a change in the distribution of a subset of T cells and an increase in the concentration of cytokines. But the mechanism of infection with SARS-CoV-2 that causes a decrease in lymphocytes and a subset of lymphocytes remains 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] In theory, in the first week, it is the virulence phase where CD8+ cells as cytotoxic T cells will be parachuted into infected cells so that a more massive proliferation of CD8+ is needed. For this reason, the body will spur CD4 + to increase its activity in order to support the proliferation of CD8 +. However, as a result, great pro-inflammatory cytokines will also be formed, including TNF–α and IL-6 which ultimately spurred a cytokine storm. At the beginning of the second week of receipts, CD4+ had already begun to decline due to feedback from cytokine storm conditions. On the other hand, CD8+ is still trying to increase its proliferation so that it still shows an increase in its amount in the blood at the beginning of week two. But then there will be '*exhausted*' events, especially in patients who have entered a severe and critical state, then in the end the number of CD8 + cells will decrease. [25-27]

5. Conclusion →6

There is a strong and meaningful positive correlation between the number of CD4+ cells and the number of CD8+ cells in COVID 19 patients at Dr. Moh Hoesin Hospital Palembang Indonesia.

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Reviewer Comment:

1→ Abstract should be showed the main of background, methods, results and conclusion of study.

- Background abstract should be showed the urgency of study and why the study important, in simple way.
- Conclusion should be wrote in simple way, specific to the main results. Conclusion in abstract should not showed statistic results.
- Keywords should be showed the main words of the study, the authors can use MeSH to develop keywords.

2→Introduction should be showed the urgency of research which supported by epidemiology data, biological interaction concept, lack of knowledge in the research and also objective of research.

3→ Authors should be wrote methods about how the study develop. Methods should be showed the design of study; population, sample and sample size of study; inclusion criteria; place of study; ethical clearence steatment; independent and dependent variable; data analysis.

4→ Authors should be wrote results with baseline characteristics subject of study, main results of study. Authors must be focused and try to make results with no more table and figure.

5→ Discussion should be explored more biological plausibility, not only showed about statistical results.

6→ Conclusion should more specific and not more showed statistical results

7→ Authors must check the references for make update references. References should no more than 10 years.

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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

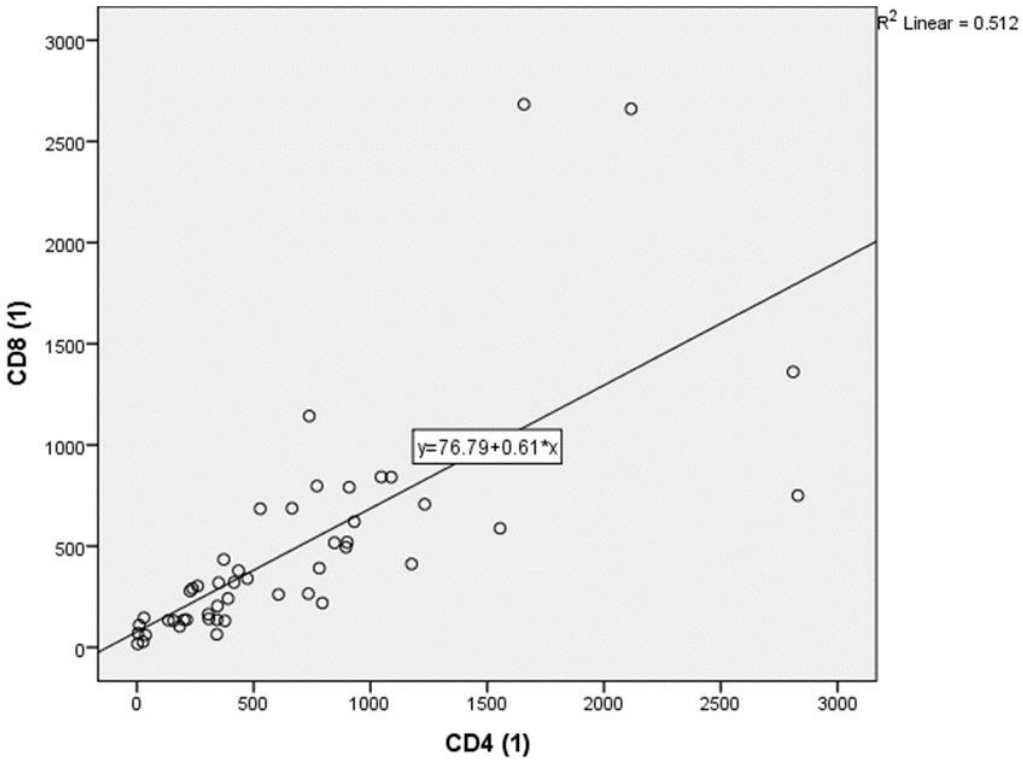

Figure 1. The relationship between the number of CD4+ and CD8+ cells

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]

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5. Conclusion

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Letter of Acceptance

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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

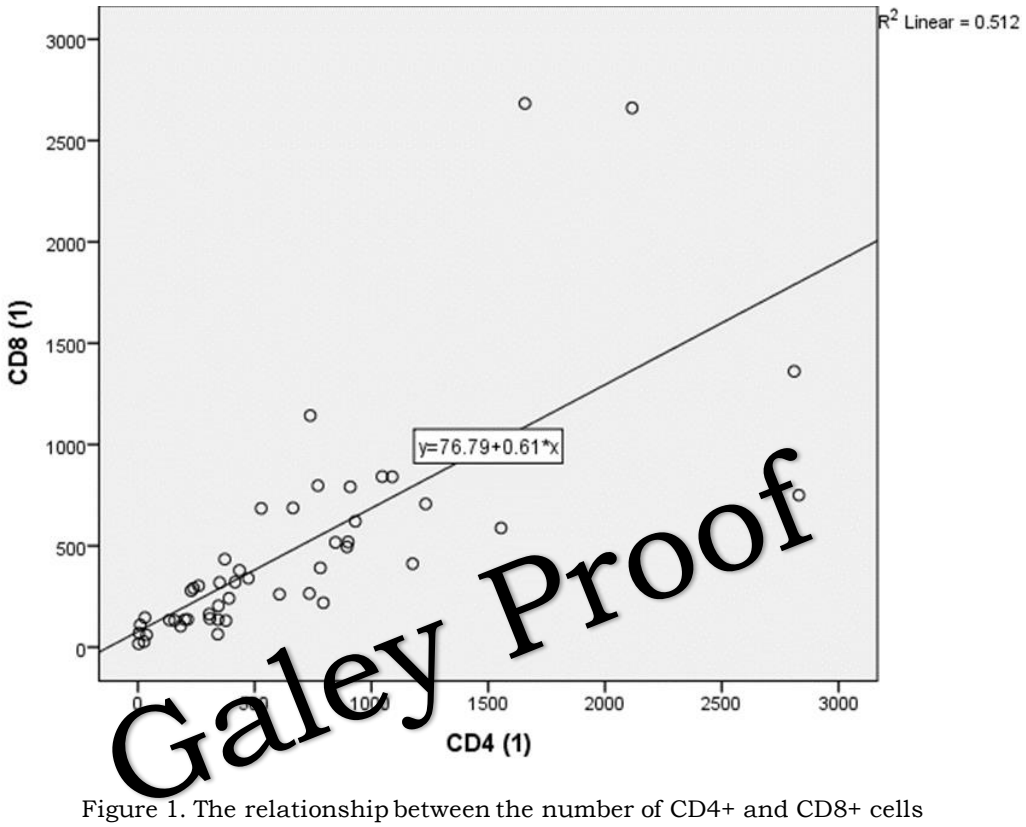

Figure 1. The relationship between the number of CD4+ and CD8+ cells

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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CERTIFICATE

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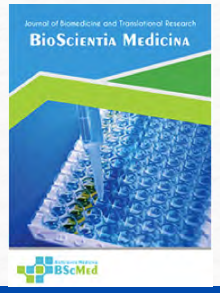

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Cordially,

Prof. Paula Magnano, PhD
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(*) Corresponding author