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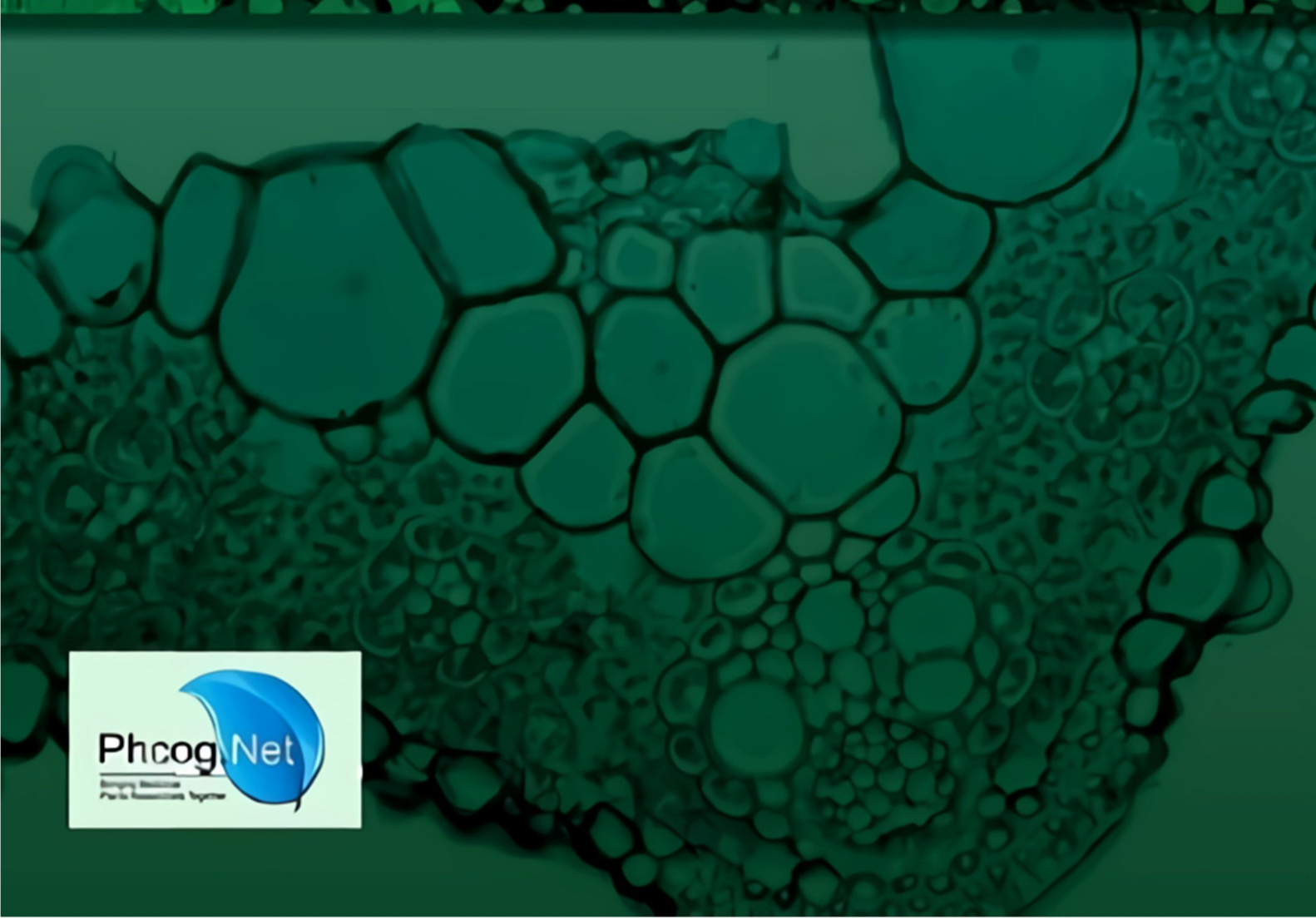

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Original Article

Differences in interleukin-6 and interleukin-17 expression in covid-19 post-mortem lung tissue biopsy compared with non-covid-19

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ABSTRACT

Background: COVID-19 has spread rapidly around the world. It is necessary to study lung tissue of post-mortem COVID19 patients to determine the molecular alteration particularly the role of IL-6 and IL-17 in causing fatality. **Objective:** This study aims to determine the differences in the expressions of IL-6 and IL-17 in lung tissue of post-mortem COVID-19 patients compared to non-COVID-19 patients. This study also aimed to analyze the correlation between the expressions of IL-6 and IL-17 in lung tissue of post-mortem COVID-19 patients. **Methods:** This research is an observational analytic study with cross-sectional approach. The samples were 15 paraffin blocks of post-mortem lung tissue biopsy of COVID-19 patients, and 15 paraffin blocks of inflammatory lung tissue biopsy or surgery of non-COVID-19 patients. IL-6 and IL-17 expressions were evaluated by immunohistochemical procedure. **Result:** There was a significant difference in the expression of IL-6 in the COVID-19 group and the non-COVID-19 group with a p-value = 0.001 ($p < 0.05$). There was a significant difference in the expression of IL-17 in the COVID-19 group and the non-COVID-19 group with p-value = 0.001 ($p < 0.05$). There was a significant correlation between the expressions of IL-6 and IL-17 in the COVID-19 group, with the Spearman coefficient value (rs) of 0.548 with $p = 0.034$ ($p < 0.05$). **Conclusion:** There are differences in the expression of IL-6 and IL-17 between COVID-19 and non-COVID-19 lung tissue. There is a significant correlation between the expressions of IL-6 and IL-17 in post-mortem lung tissue of COVID-19 patients.

Key words: Biopsy, COVID-19, IL-6, IL-17, Post mortem lung tissue.

INTRODUCTION

Since December 2019, Corona Virus Disease (COVID-19) caused by Severe Acute Respiratory Syndrome Corona Virus 2 (SARS CoV-2) has spread rapidly around the world. SARS-CoV2 is an RNA (ribonucleic acid) virus with a new variant belonging to the Coronaviridae family which was first described in February 2020.[1] The World Health Organization stated that until March 2021, the number of confirmed cases was 125 million with a death toll of 2.8 million. COVID-19 has also had a negative impact on the global economy and health system. Lack of knowledge regarding the characteristics and pathogenesis of the SARS COV-2 virus causes difficulties in controlling the course of the COVID-19 disease. It is necessary to conduct research on lung tissue of post-mortem COVID19 patients to determine the molecular alteration that plays a role in causing fatality.

The pathogenesis of COVID-19 can generally be categorized into three successive and overlapping phases, namely the pulmonary phase, the proinflammatory phase and the prothrombotic phase.[2] In the proinflammatory phase, SARS-CoV-2 causes the release of proinflammatory cytokines in very large quantities that cause interstitial pneumonia and acute respiratory distress syndrome (ARDS). In a more advanced state will develop sepsis and cytokine storm (cytokine storm) with hypercoagulability and multiorgan dysfunction.[2,3] Several types of cytokines that play a role in the pathogenesis of COVID-19 are IL-1β, IL-2, IL-4, IL-6, IL-8, IL12, IL-17, G-CSF, GM-CSF, IFNγ, MCP-1 and TNFα. Cytokines IL-6 and IL-17 are known to play an important role and influence disease fatality, which levels of both are known to be elevated in blood.[1,4-6]

Interleukin-6 (IL-6) is one of the cytokines that is activated in the presence of infection or injury. I-6 is secreted by various cell types and plays a role in the regulation of various physiological processes. Elevated of IL-6 serum levels are associated with an inflammatory response, respiratory failure and affect mortality in COVID-19 patients.[7-9] Interleukin-17 (IL-17) is a cytokine synthesized by Th17 lymphocytes and is increased in inflammatory processes and autoimmune diseases. IL-17 is a proinflammatory cytokine that plays a role in tissue damage, physiological stress, and infection.[5,10]

A number of studies have been carried out through blood serum analysis to study the important role of IL-6 and IL-17 in the pathogenesis of COVID-19, but lack studies to analyze the role of IL-6 and IL-17 in lung tissue of patients with COVID-19. This study aims to determine the differences in the expression of IL-6 and IL-17 in lung tissue of post-mortem

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COVID-19 patients compared to non-COVID-19 patients and to analyze the correlation between the expression of IL-6 and IL-17 in lung tissue of post-mortem COVID-19 patients.

MATERIAL AND METHODS

The design of this research is an observational analytic with cross-sectional approach. This research is a branch of research titled 'Multi-organ pathological finding in COVID-19 infection through post-mortem core biopsy' and has received ethical approval from the Health Research Ethics Committee of Dr. Soetomo general hospital number 0022/KEPK/VII/2020.

The number of research samples is 30, consisting of 15 paraffin blocks of post-mortem pulmonary tissue biopsy of patients with COVID-19 and 15 paraffin blocks of pulmonary tissue biopsy or surgery of non-COVID-19 pneumonia patients. IL-6 expression was evaluated by an immunohistochemical procedure using IL-6 antibody GeneTex Antibodies Rabbit Polyclonal antibody, unconjugated (GTX17623). Antigen retrieval using pH 6, with a dilution of 1:100. IL-17 expression was also evaluated by an immunohistochemical procedure using anti-GeneTex Antibodies Rabbit Recombinant-Human IL-17 (IL-17A) polyclonal antibody, unconjugated (GTX31174) antibody, with a concentration of 0.25 g/ml. The expression of IL-6 was positive for brown color in the cytoplasm of lymphocytes and macrophages, while the expression of IL-17 was positive for brown color in the cytoplasm of lymphocyte cells. The assessment is carried out in five fields of view with high power fields. The number of positive cells is calculated as a percentage. The assessment was carried out by two pathologists in a double-blind manner and then an average of the two was made. Analysis of expression differences was done with independent T-test. Analysis of correlation was done with Spearman correlation test. Statistic result is significant if $p < 0.05$.

RESULT

The data obtained in this study showed the sex distribution in the COVID-19 group, the number of subjects being male was 8 people (53%) and women were 7 people (47%). While in the non-COVID-19 group, the number of male subjects was 11 people (73%) and 4 women (27%).

Age data showed that in the COVID-19 group, the highest number was from the 41-50-year-old and 51-60-year age group, each of which amounted to 5 people (33.3%). Meanwhile, from the non-COVID-19 group, the highest number was in the age range of 61-70 years, namely 5 people (33.3%).

The results of this study showed the mean expression of IL-6 in the COVID-19 group was 80.67% ± 7.03, while in the non-COVID-19 group it was 21.50 ± 11.60. The difference between the two was then assessed using the Independent T test. The results of statistical analysis showed a significant difference between the expression of IL-6 in the COVID-19 group and the non-COVID-19 group with p value = 0.001 ($p < 0.05$).

The results of IL-6 expression in the COVID-19 and non-COVID-19 groups are presented in table 3. The average percentage of IL-6 expression in the COVID-19 group is higher than the non-COVID-19 group.

The results of this study showed the mean expression of IL-17 in the COVID-19 group was 75.33% ± 14.93, while in the non-COVID-19 group it was 45.67% ± 17.31. The difference between the two was then assessed using the Independent T test. The results of statistical analysis showed a significant difference between the expression of IL-17 in the COVID-19 group and the non-COVID-19 group with p value = 0.001 ($p < 0.05$).

Table 1: Distribution COVID-19 and non COVID-19 groups by gender.

	COVID-19 (n)	Non COVID-19 (n)
Male	8	11
Female	7	4

Table 2: Distribution COVID-19 and non-COVID-19 groups by age.

	COVID-19		Non COVID-19	
	Number	Percentage	Number	Percentage
< 10 years	0	0%	1	6.67%
11-20 years	0	0%	1	6.67%
21-30 years	1	6.67%	0	0%
31-40 years	3	20%	1	6.67%
41-50 years	5	33.3%	3	20%
51-60 years	5	33.3%	3	20%
61-70 years	1	6.67%	5	33.3%
> 70 years	0	0%	1	6.67%
Total	15	100%	15	100%

Table 3: Table of results of the assessment of IL-6 expression in the COVID-19 and non-COVID-19 groups.

Groups	n	Avarage (%)	SD	Min	Max	p
COVID-19	15	80.67	7.03	70	90	0.001
Non COVID-19	15	21.50	11.60	7.5	55	

Table 4: Table of results of the assessment of IL-17 expression in the COVID-19 and non-COVID-19 groups.

Groups	n	Average (%)	SD	Min	Max	P
COVID-19	15	75.33	14.93	30	90	0.001
Non COVID-19	15	45.67	17.31	20	75	

Table 5: Correlation of IL-6 and IL-17 expression in all samples.

		IL-17 expression
IL-6 expression	r_s	0.779
	p	0.001
	n	30

Table 6: Correlation of IL-6 and IL-17 expression in the COVID-19 patient group.

		IL-17 expression
IL-6 expression	r_s	0.548
	p	0.034
	n	15

The results of IL-17 expression in the COVID-19 and non-COVID-19 groups are presented in table 4. The average percentage of IL-17 expression in the COVID-19 group is higher than the non-COVID-19 group. Figure 2 shows an overview of IL-17 expression in the COVID-19 and non-COVID-19 groups.

The correlation between the expression of IL-6 and IL-17 in lung tissue of COVID-19 and non-COVID-19 patients was statistically tested using the Spearman correlation test. The results of the analysis showed a significant correlation between the expression of IL-6 and IL-17 in all samples (COVID-19 and non-COVID-19 groups) with a Spearman correlation coefficient (rs) of 0.779 with $p = 0.001$ ($p < 0.05$), which means that the higher the expression of IL-6, the higher the expression of IL-17.

In the group of COVID-19 patients, a significant correlation was found between the expression of IL-6 and IL-17. The results of statistical analysis using the Spearman correlation test showed the Spearman coefficient (rs) of 0.548 with $p = 0.034$ ($p < 0.05$) which means that the

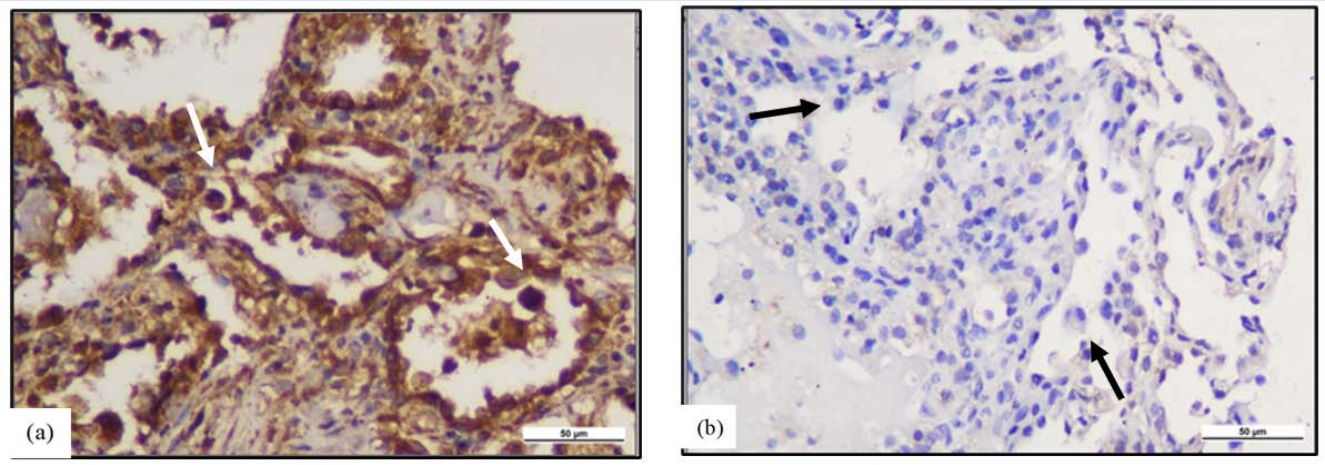

Figure 1: IL-6 expression in the COVID-19 and non-COVID-19 groups, magnification 400x. (a) IL-6 is positively expressed in lung tissue of COVID-19 patients (white arrow), (b) IL-6 is negatively expressed in lung tissue of non-COVID-19 patients (black arrow).

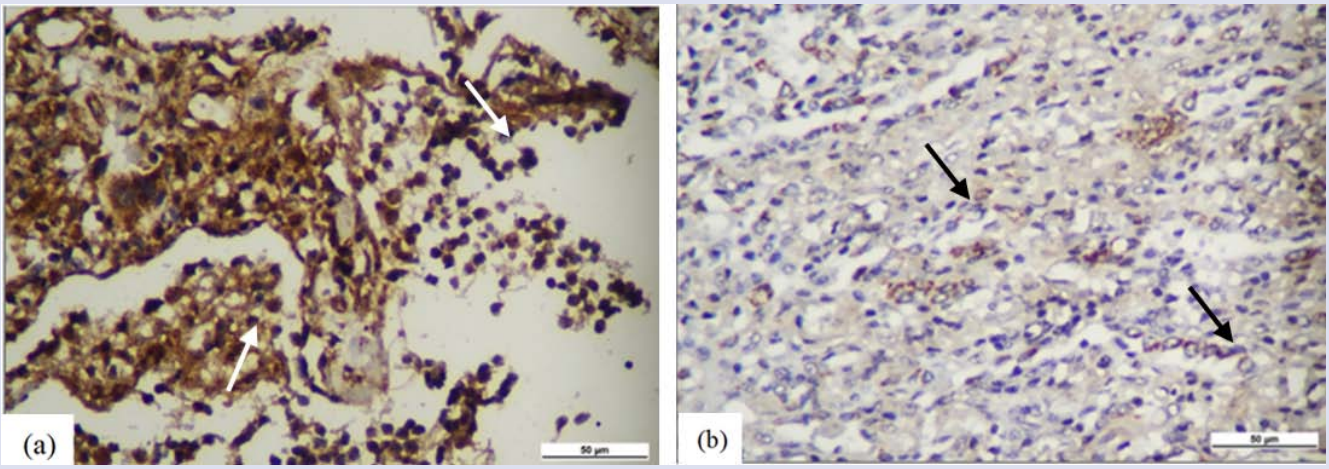

Figure 2: IL-17 expression in the COVID-19 and non-COVID-19 groups, magnification 400x. (a) IL-17 is positively expressed in lung tissue of COVID-19 patients (white arrow), (b) IL-17 is negatively expressed in lung tissue of non-COVID-19 patients (black arrow).

high expression of IL-6 in the tissue will be directly proportional to the expression of IL-17.

DISCUSSION

The data obtained in this study shows the sex distribution of COVID-19 cases, where the incidence of COVID-19 in men (53%) and women (47%) is almost the same. The incidence of disease and fatality in males was found to be slightly higher than that of females. This is in line with WHO data where the percentage of male sufferers is more (58%) in the UK 57% and 51.1% in China.[10-12]

Almost the same figure was also found in the incidence of COVID 19 in Indonesia. Several studies have shown higher morbidity and mortality rates in men, namely 58.94%,[13] 56.5% with a fatality rate of 63.8%.[14] Several studies have linked this event to several factors including sex hormones, the X chromosome (playing a role in high innate and adaptive immunity) and high expression of ACE 2 receptors, and lifestyle. Men smoke and consume alcohol more often.[15,16]

The age range of the sample is between 5 and 88 years, with the mean age of the entire sample being 48.93 years. From these data, it was found that in the COVID-19 group, the highest number was from the 41-50-year-old and 51-60-year age group, each of which amounted to 5 people (33.3%). This is slightly different from several other studies where the highest fatality rate was found in the age range > 60 years, followed by the 40-59-year age group. While the smallest mortality rate was obtained from the age group < 10 years.[11,14] The high mortality rate in the old age group is most likely due to the weak immune system in old age and the number of comorbid diseases that aggravate the course of COVID-19. In this study, the highest number was from the age group of 41-50 years and 51-60 years. This is different from other studies because this study did not assess the proportion of fatalities in each age group.

In addition to old age and male gender, several other risk factors that play a role in increasing mortality rates in COVID patients are the presence of co-morbidities such as diabetes, cardiovascular, cerebrovascular and kidney diseases, and obesity.[15,17] Several socioeconomic conditions can also play a role, for example lack of socioeconomic conditions, high levels of air pollution and diurnal temperature variations.[17]

The data obtained from this study showed that the mean expression of IL-6 in the COVID-19 group was significantly higher than in the non-COVID-19 group. Previous studies have also shown high expression of IL-6 in lung tissue of COVID-19 patients, and is a predictor of fatality and disease progression.[7,9,18,19]

Interleukin-6 is a pleiotrophic cytokine that is activated in the presence of infection or injury, one of which is a viral infection. Interleukin-6 is secreted by various cell types (eg: T lymphocytes, macrophages, and fibroblasts) and plays a role in the regulation of various physiological processes.[9] The role of IL-6 in the inflammatory process including COVID infection is like a double-edged sword, because it has two effects, namely pro- and anti-inflammatory. There are two pathways in the IL-6 signaling process, namely the classical pathway and the IL-6 signal trans pathway. The classical pathway is considered the anti-inflammatory pathway whereas the signal trans pathway is the pro-inflammatory pathway. Therefore, in various inflammatory conditions and autoimmune diseases, the role of the IL-6 signaling trans pathway is that inhibiting this process is needed to relieve inflammation and damage that occurs.[20] One of the roles of IL-6 as part of the pro-inflammatory function is in the activation and differentiation of Th17, and induces the expression of granzyme B and perforin on CD8 T lymphocytes that can eliminate the virus. Activation of these cytotoxic T cells will stimulate the release of TNF- and IFN-Ɣ which causes neutrophil migration. In addition, IL-6 also plays a role in thermoregulation (as an endogenous pyrogenic cytokine) and amplifies the immune response to viral infections. The IL-6 signal is known to induce the production of IL-27 by monocytes and macrophages in the respiratory tract, thereby stimulating T cell maturation in the lungs.[20] Interleukin 6 has also been shown to be associated with inflammatory responses in the acute phase, including CRP and LDH.[21] On the other hand, the anti-inflammatory function of IL-6 plays a role in the progression of viral infection, thereby causing viral persistence in the host. Interleukin-6 stimulates the Th2 response while inhibiting Th1 proliferation through two mechanisms. First, by stimulating CD4 T cells to secrete IL-4 which will stimulate Th2 and suppress the production of IFN-Ɣ by CD4 T cells and cause Th1 polarization (antiviral response). Interleukin-6 will cause Th17 differentiation which will then produce IL-17 which will increase the expression of anti-apoptotic molecules so that the virus is stronger and can survive.[19] A study proved that increased expression of IL-6 in lung tissue indicates the severity of COVID-19 sufferers.[22]

Interleukin-17 plays a role in the pathogenesis of ARDS by increasing the infiltration of neutrophils into the lung. Increased signaling of IL-17A and Th17 or regulatory T cells (Treg) is known to be positively correlated with disease severity in MERS infection, where the cause is a type of virus that belongs to the same family as MERS. The overexpression of Th17 cells and the excessive cytotoxic effect of CD8+ T cells will cause tissue damage in COVID-19 patients with pneumonia. Like IL-6, high expression of IL-17A in lung tissue is also directly proportional to lung inflammation and poor outcomes (ARDS) and multi-organ dysfunction.[23,24]

Various studies have shown the important role of IL-17A as a regulator of PMN infiltration. IL-17 is known to play a role in neutrophil maturation and differentiation by increasing the release of granulocyte-colony stimulating factor (G-CSF). This situation will cause the differentiation of hematopoietic progenitor cells CD34 into neutrophils. In addition, IL-17 can stimulate granulopoiesis markers and other chemokines, such as Growth-regulated Oncogene-α (GRO-α) which will regulate neutrophil penetration into tissues. Interleukin-17 also plays a role in the release of cytokines and other inflammatory chemokines such as IL-1, IL-6, TNF-α, macrophage inflammatory protein-2 (MIP-2), IL-8, Interferon-inducible protein-10 (IP-10). All these molecules will be used by neutrophils in the process of chemotaxis.[25]

According to Hou *et al*., IL-17 can also increase the expression of antiapoptotic molecules that increase the survival of virus-infected cells and block the process of destruction by cytotoxic T cells.[26] Therefore, the role of IL-17 in COVID inflammation is important in amplification of the inflammatory process.[25]

The results of this study showed that the mean expression of IL-17 in the COVID-19 group was significantly higher than the non-COVID-19 group. Several previous studies showed high IL-17 expression in lung tissue of COVID-19 patients and was a predictor of fatality and disease progression.[23-27] A similar study conducted by Avezedo *et al*., which assessed the expression of IL-17 and IL-8 in post-mortem lung tissue of patients with COVID-19 also showed results that were in line with this study.[28]

The results of the analysis of this study showed that there was a positive and significant correlation between the expression of IL-6 and IL-17 in all samples (COVID-19 and non-COVID-19 groups) as well as when analyzed only in the COVID-19 group. The COVID-19 group showed a higher correlation. This phenomenon can be seen in general that the pathogenesis of COVID-19 may be different from other infectious processes. In COVID-19, there is an exaggerated immune response that is characteristic of this disease. The state of hypercytokinemia or what is called a cytokine storm is a collection of symptoms caused by the activation of T lymphocytes, macrophages and the release of various cytokines which then activate other immune cells. In the laboratory, cytokine storm is characterized by an increase in various proinflammatory cytokines such as IL-1, IL-6, Il-12, IFN-Ɣ. Measurement of these levels, especially IL-6 is considered useful as a predictor of fatality rates and the need for respiratory equipment, and can be used as a potential therapeutic target.[7,9,19]

The SARS-CoV2 virus which is the etiology of COVID-19 has a surface protein, namely the surface spike (S) protein, which will bind to the Angiotensin Converting Enzyme-2 (ACE-2) receptor found in pulmonary alveolar epithelial cells to enter the body. The ACE-2 receptor is very important in viral virulence, because it has been shown that cells that do not have this receptor are resistant to viral infection. Angiotensin Converting Enzyme-2 is not only expressed in the respiratory tract, but also in the small intestine, pancreas, kidney, heart, esophagus, bladder and brain. This has led to multi-organ involvement in COVID-19. Under normal conditions, ACE-2 functions to cause the conversion of angiotensin II to angiotensin 1-7 in the renin-angiotensin-aldosterone system (RAA system). Various studies have reported increased levels of Angiotensin II in COVID-19 patients compared to healthy individuals, which is associated with viral load and lung damage. This situation is caused by the virus binding to ACE-2, so that Angiotensin II cannot be converted, accumulates and causes an imbalance in the RAA system. Angiotensin II buildup will cause a change in equilibrium towards a proinflammatory state.[19] In the absence of ACE-2, angiotensin II will bind to the angiotensin I receptor which will cause an oxidative stress cascade, resulting in the formation of Reactive Oxygen Species (ROS) and an increase in IL-6 expression. On the other hand, the increased expression of IL-6 will also increase the expression of angiotensin I receptors and attach to endothelial cell walls and cause cellular and vascular inflammation. Interleukin-6 and angiotensin II will cause an increase in the expression of each other continuously so that over time it will aggravate the state of oxidative stress.[19]

The role of IL-6 in inflammatory processes including COVID infection is like a double-edged sword, because it has two effects, namely pro- and anti-inflammatory.[9,19] In pro-inflammatory, one of the functions of IL-6 is in the activation and differentiation of Th17 and the induction of granzyme B and perforin in CD8 T lymphocyte cells. Interleukin-6 causes the production of IL-17 which will further increase the expression of antiapoptosis molecules leading to increasing the survival of virus-infected cells and blocking the process of digestion by cytotoxic T cells.[26] Interleukin-17 mainly causes neutrophil migration to the lungs thus causing tissue damage during the inflammatory process.[19] Interleukin-17 also plays a role in the release of cytokines and other inflammatory chemokines such as IL-1, IL-6, TNF-α, macrophage

inflammatory protein-2 (MIP-2), IL-8, Interferon-inducible protein-10 (IP-10).[19]

The synergistic interaction between IL-17A and IL-6 plays an important role in the formation of pulmonary fibrosis and imbalances of the respiration system. IL-6 not only plays a role in the differentiation of T helper (Th) cells into Th17 cells through RORγt which is the JAK-STAT3 pathway but also in the process of pulmonary fibrosis (causing collagen deposition) due to the function of epithelial cells and fibroblasts that are aberrant (works synergistically with IL-8).[6,29]

CONCLUSION

There are significant differences between IL-6 and IL-17, which are higher expressed in the lung tissue of covid-19 patients than the lung tissue of the non-COVID-19 group. There was also a strong correlation between IL-6 and IL-17 in the lung tissue of COVID-19 patients, as well as in the entire sample. Although not a single factor, IL-6 and IL-17 play a role in the pathogenesis of COVID-19.

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ETHICS AND CONSENT

This research is a branch of research titled 'Multi-organ pathological finding in COVID-19 infection through post-mortem core biopsy' and has received ethical approval from the Health Research Ethics Committee of Dr. Soetomo general hospital number 0022/KEPK/VII/2020.

CONFLICTS OF INTEREST/PLAGIARISM REPORT

There are no conflicts of interest in this research.

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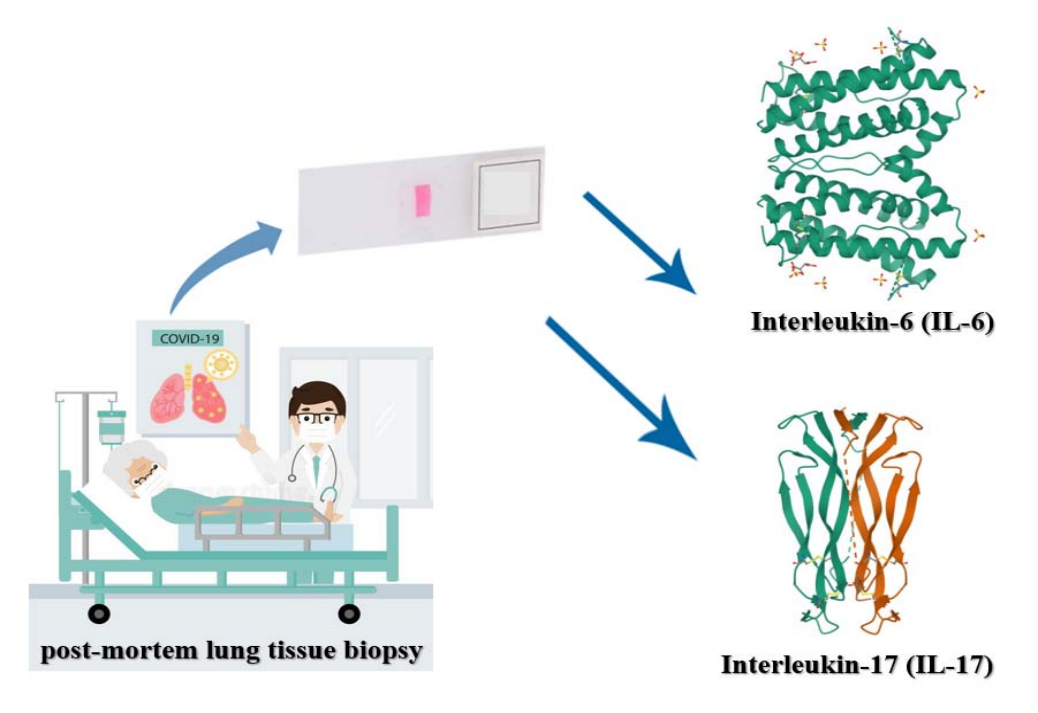

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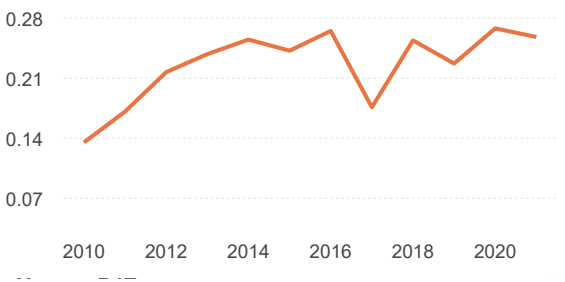

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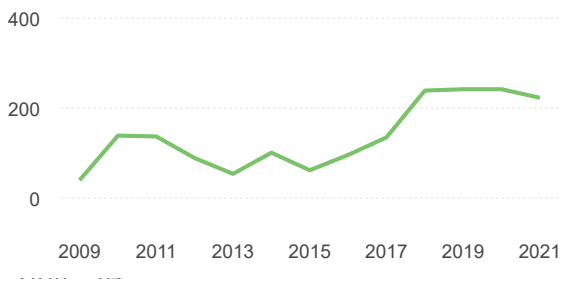

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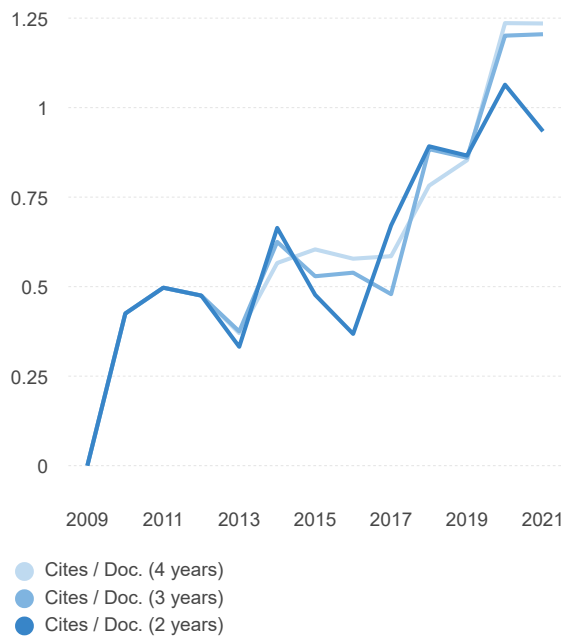

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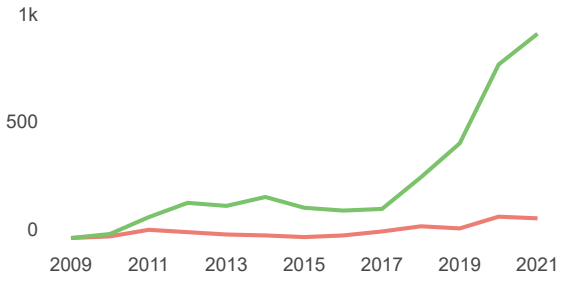

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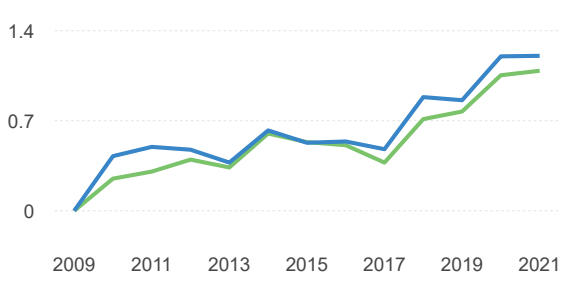

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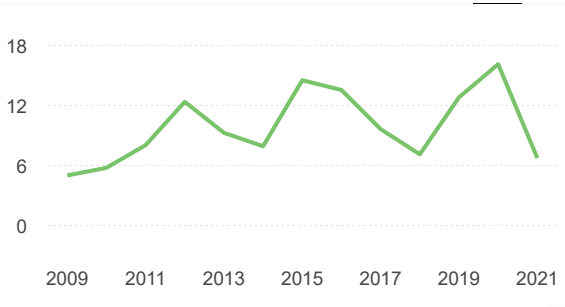

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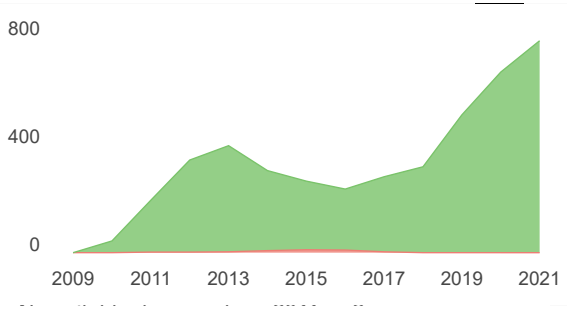

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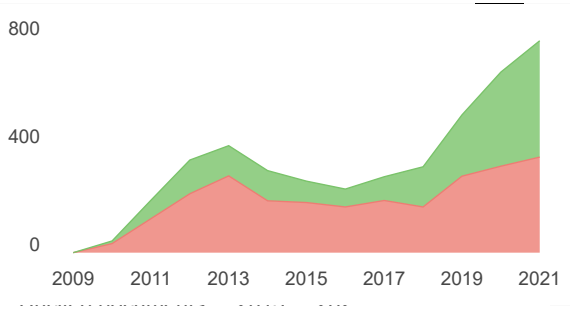

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Berlaku sampai	:	*21 Januari 2024*
Peneliti Utama	:	Dr. Etty Hary Kusumastuti, dr., Sp.PA (K)., FIAC
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Instalasi/Tempat Penelitian	:	RSUD Dr. Soetomo

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Prof. Dr. Hendy Hendarto dr., SpOG(K)
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Dra. Siti Farida SpFRS. Apt
Sekretaris Panel 1