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THE TOTAL LEUKOCYTE COUNT OF ELDERLY PATIENTS CONFIRMED COVID-19 WITH/WITHOUT A VENTILATOR IN A SURABAYA GENERAL HOSPITAL IN 2021

JUMLAH SEL LEUKOSIT PADA PASIEN LANSIA TERKONFIRMASI COVID-19 DENGAN DAN TANPA VENTILATOR DI RUMAH SAKIT UMUM SURABAYA TAHUN 2021

Research Report
Penelitian

Safira Indah Fitriani, Nur Septia Handayani*, Erlinda Widyastuti, Anita Kurniati

Department of Health, Division of Medical Laboratory Technologist, Faculty of Vocational Studies, Universitas Airlangga, Indonesia

A B S T R A C T

Background: *Coronavirus is a virus that attacks the immune system, especially the human respiratory system. The elderly are at high risk of being infected with Coronavirus Disease-19 (COVID-19), and as they get older, they are at risk of experiencing severe symptoms when infected with COVID-19. Leukocytes play a role in the immune system against foreign objects. The leukocyte count will decrease in the elderly. On the other hand, the increase of leukocytes plays a role as a clinical sign that is useful to be a predictor of body immunity when infected with COVID-19.* ***Purpose:*** *To determine the total leukocyte count in elderly patients that were confirmed COVID-19 and hospitalized with and without a ventilator.* ***Method:*** *This study was a cross-sectional design study involving 93 elderly patients in General Hospital Surabaya.* ***Result:*** *The results showed no difference in the total leukocyte count in elderly hospitalized patients with and without a ventilator (p-value = 0.756). Age above 70 years old increases the risk of patients requiring a ventilator up to 1.7 times compared to patients under 70 years old. The highest leukocyte count was 20.880/mm^3, and the lowest was 3.760/mm^3. The ratio of leukocyte count in elderly patients with a ventilator group is 1 : 3 for low and high leukocyte counts, respectively.* ***Conclusion:*** *Leukocyte count is an important parameter as the predictor of the progression of the disease and helps in the decision regarding treatment strategy to prevent the cytokine storm.*

A B S T R A K

Latar belakang: Virus Corona merupakan virus yang menyerang sistem kekebalan tubuh, terutama pada sistem pernapasan manusia. Lansia merupakan kelompok yang berisiko tinggi terinfeksi *Coronavirus Disease-19* (COVID-19), karena seiring bertambahnya usia maka risiko untuk mengalami gejala parah saat terinfeksi COVID-19 akan meningkat. Leukosit memiliki peran dalam sistem kekebalan tubuh terhadap benda asing. Pada kelompok lanjut usia (lansia), jumlah leukosit akan menurun, namun sebaliknya peningkatan jumlah leukosit berperan sebagai tanda klinis prediktor imunitas tubuh saat virus Corona masuk ke tubuh. **Tujuan:** Untuk mengetahui jumlah leukosit total pada pasien lansia terkonfirmasi COVID-19 dan dirawat inap di rumah sakit dengan dan tanpa ventilator. **Metode:** Penelitian ini merupakan penelitian dengan desain *cross-sectional* yang melibatkan 93 pasien lansia dari salah satu rumah sakit umum di Surabaya. **Hasil:** Hasil penelitian menunjukkan tidak ada perbedaan jumlah leukosit total pada pasien lansia rawat inap dengan dan tanpa ventilator (*p-value* = 0,756). Usia diatas 70 tahun meningkatkan risiko pasien membutuhkan ventilator hingga 1,7 kali dibandingkan pasien dibawah 70 tahun. Jumlah leukosit tertinggi yaitu 20.880/mm^3 dan terendah 3.760/mm^3. Rasio jumlah leukosit pada pasien lansia dengan kelompok ventilator adalah 1 : 3 untuk jumlah leukosit rendah dan tinggi. **Kesimpulan:** Jumlah leukosit merupakan parameter penting sebagai *predictor* perkembangan penyakit dan membantu dalam pengambilan keputusan mengenai strategi pengobatan untuk mencegah badai sitokin.

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Correspondence:
Nur Septia Handayani

Email:
nur.septia.h@vokasi.unair.ac.id

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INTRODUCTION

In the past three years, *Coronavirus Disease-19* (COVID-19) has been the most significant health problem in the world, including in Indonesia. In February 2020, WHO introduced COVID-19 as the name of a new disease for the first time. As time passed by, COVID-19 still spread worldwide. On October 5th, 2022, the cases of COVID-19 in the world reached more than 610 million and caused more than 6.5 million deaths. Meanwhile, in Indonesia, COVID-19 cases reached more than 6.4 million and caused more than 150 thousand deaths (Satgas COVID-19, 2022; WHO, 2020). On June 20th, 2021 the National COVID-19 task force reported that the highest number of death was attributed to the city of Surabaya with a total of 1.382 death from 12.074 deaths in Indonesia (WHO, 2021).

Coronavirus is a virus that attacks the immune system, especially the human respiratory system. Elderly people have a high risk of being exposed to COVID-19 because of the decrease in their immunity system. Once the elderly are confirmed positive for COVID-19, they are more likely to have severe symptoms. The severe symptoms mean that the elderly might need hospitalization, intensive care, or a ventilator to help them breathe. Otherwise, they might even die. The risk increases for people in their 50s and keeps on increasing in their 60s, 70s, and 80s. It also might worsen if the elderly have comorbid or chronic health conditions (CDC, 2020; Ganie, 2020).

The patient confirmed COVID-19 would carry out several medical examinations, such as the white blood cell count examination (Dhinata, 2021; Ministry of Health of the Republic of Indonesia, 2020). Leukocyte or *White Blood Cell* (WBC) is commonly known to have an essential role in immunity and host response to infection, including in the elderly. Some studies found out that the evaluation of leukocytes and the differential count played a significant role in supporting the COVID-19 diagnosis and predicting the severity of the disease. The elevated white blood cell count could associate with hospital discharge rates and deaths in COVID-19 patients. Beside that, the leukocyte variations could contribute to increased clinical severity and directly indicate the poor prognosis of SARS-CoV-2 infections. Meanwhile, in the elderly, the total leukocyte count will decrease slightly as people age (Aminzadeh and Parsa, 2011; Dhinata, 2021; Pijls et al., 2021; Selim, 2020; Zhu et al., 2021). In this study, we investigated the leukocyte count of elderly patients who were confirmed COVID-19 based on the treatment with/without a ventilator in one of the general hospitals in Surabaya in 2021.

MATERIAL AND METHOD

This study was a *cross-sectional* study using secondary data from one of the general hospitals in Surabaya involving 93 elderly patients that were confirmed COVID-19 in 2021. The inclusion criteria for the subject were (1) Hospitalized patients that were confirmed COVID-19 in January to December 2021, (2) Patients' ages ranging from 60 years and over, and (3) Having the data results of leukocyte count. The elderly patient in this study was divided into two rooms (1) The patient with severe symptoms and using a ventilator in the COVID-19 ICU room the 6th floor and (2) The patients with moderate symptoms without a ventilator in isolation COVID-19 room, the 4th floor. The leukocyte count was analyzed using Sysmex XN-500. The method to analyze leukocyte count using Sysmex XN-500 is fluorescence cytometry. The normal range of leukocyte counts for adults from 13 years and over is 4.500–13.500/mm^3.

The data in this study will be presented in tables and graphs. Categorical data are presented in frequency and percentage (gender, productive age, high-risk age, and leukocyte count), while numerical data are presented in median (min-max). *Chi-square* and *Fisher exact* test were used to determine the difference between categorical variables. For the leukocyte count as a categorical variable, cells were combined between low and normal to meet the requirements of the fisher exact test. *Mann-Whitney* test was used to determine the differences between numerical variables (age and leukocyte count). The determination of odds ratio and 95% confidence interval used binary logistic analysis for dichotomy outcome (with a ventilator and without a ventilator). The analysis used the SPSS Ver. 26.

RESULT

Characteristics elderly patients confirmed COVID-19

This study involved data from 93 elderly patients that were confirmed COVID-19 from January 2021 to December 2021 and hospitalized at X general hospital Surabaya. The 93 patient were elderly patients aged 60 years and over who completed the blood count examination. The majority of the elderly patients confirmed COVID-19 in 2021 was male for 53 (57%) patients with the majority's age ranging from 65 to 69 years for 23 (43%), while the total number of female patients was 40 (43%) patients with 16 patients (40%) whose age ranged from 60-64 years (Table 1).

Table 1. The distribution of elderly patients confirmed COVID-19 based on age group and gender

Age (years old)	Male n (%)	Female n (%)
60-64	18 (34)	16 (40)
65-69	23 (43)	10 (25)
70-74	7 (13)	4 (10)
75-79	3 (6)	5 (12)
80-84	2 (4)	4 (10)
85-89	0 (0)	1 (3)
Total	53 (100)	40 (100)

The elderly patients confirmed COVID-19 were divided into two-room care in X general hospital Surabaya based on the patient's clinical history. The first room was ICU COVID-19 Isolation Room on the 6th floor. In this room, 16 (17%) elderly patients had critical conditions and severe COVID-19 symptoms, and were treated with a ventilator. The second room was COVID-19 Isolation Room on the 4th floor. In this room, 77 (83%) elderly patients had moderate COVID-19 symptoms and needed special care from healthcare workers, but were treated without a ventilator (Figure 1).

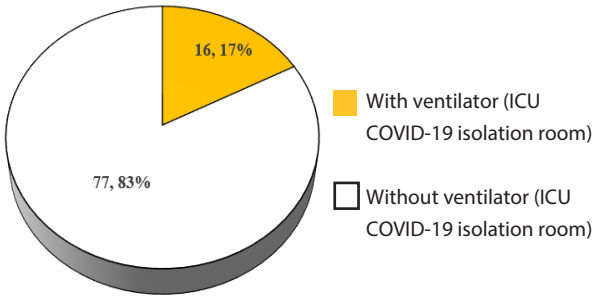

Figure 1. The distribution of elderly patients based on the treatment

The distribution of leukocyte count based on age group and gender

Table 2 displays that most elderly patients had normal leukocyte counts in males and females. The normal range of leukocyte count is 4.500-13.500/mm^3. The age ranging from 60 to 64 years old is known as the elderly productive age, while the age over 70 is known as a high-risk age, especially with health association (Ministry of Health, 2021). Further, the results of the study revelead some elderly patients with leukocyte count below normal (<4500/mm^3) and above the normal range (>13500/mm^3). Three elderly patients (one male at elderly productive age and two females at high-risk age) have a total leukocyte count below normal. In comparison, 19 patients (9 males and 10 females, the majority in the productive age range) have a total leukocyte count above normal.

The distribution of leukocyte count in elderly patients based on a ventilator usage

The detailed overview of leukocyte count distribution of elderly patients based on the ventilator usage can be seen in Figure 2 and Figure 3. From the total number of elderly patients with a ventilator involved in this study, 16 patients and the rest of the 77 elderly patients did not use the ventilator. The majority of leukocyte count values in both groups was in the normal range, but low and high leukocyte count values were discovered in both groups. The critical leukocyte count values below and above the normal range (4.500-13.500/mm^3) in both groups are not much different. The highest leukocyte count value in elderly patients with a ventilator group was 19.720/mm^3 at 66 years old, while in elderly patients without a ventilator was slightly higher or 20.880/mm^3 at 79 years old patient. The same condition can be found in the lowest leukocyte count value in elderly patients. The lowest leukocyte count value in the group of elderly patients with a ventilator was 3.760/mm^3 at 81 years old patient, while in the group of elderly patients without a ventilator was 3.900/mm^3 at 78 years old patient.

The majority of elderly patients confirmed COVID-19 with a ventilator were female, with a ratio of 1 : 1.28 for males and females, respectively. The highest percentage among the age group of elderly patients with a ventilator is the patients in the high-risk age group or aged 70 years old and over (23.1%). The results of statistical analysis in this study showed that the distribution of leukocyte count between elderly patients with a ventilator group and elderly patients without a ventilator group was not significantly different (*p-value* 0.756). This study indicated that the risk of female elderly patients requiring a ventilator treatment was 1.9 times higher than the risk of male elderly patients. Besides that, the risk of elderly patients aged 70 years and over requiring a ventilator treatment was 1.5 times higher than the risk of elderly patients below 70 years old.

Table 2. The distribution of categorical total leukocyte count based on age group and gender

Age group (years old)	Total leukocyte count		
	Low n (%)	Normal n (%)	High n (%)
Male			
60-64	1 (100)	14 (32)	3 (33,5)
65-69	0 (0)	20 (46)	3 (33,5)
70-74	0 (0)	5 (12)	2 (22)
75-79	0 (0)	2 (5)	1 (11)
80-84	0 (0)	2 (5)	0 (0)
85-89	0 (0)	0 (0)	0 (0)
Total	1 (100)	43 (100)	9 (100)
Female			
60-64	0 (0)	12 (43)	4 (40)
65-69	0 (0)	7 (25)	3 (30)
70-74	0 (0)	3 (11)	1 (10)
75-79	1 (50)	3 (11)	1 (10)
80-84	1 (50)	2 (7)	1 (10)
85-89	0 (0)	1 (3)	0 (0)
Total	2 (100)	28 (100)	10 (100)

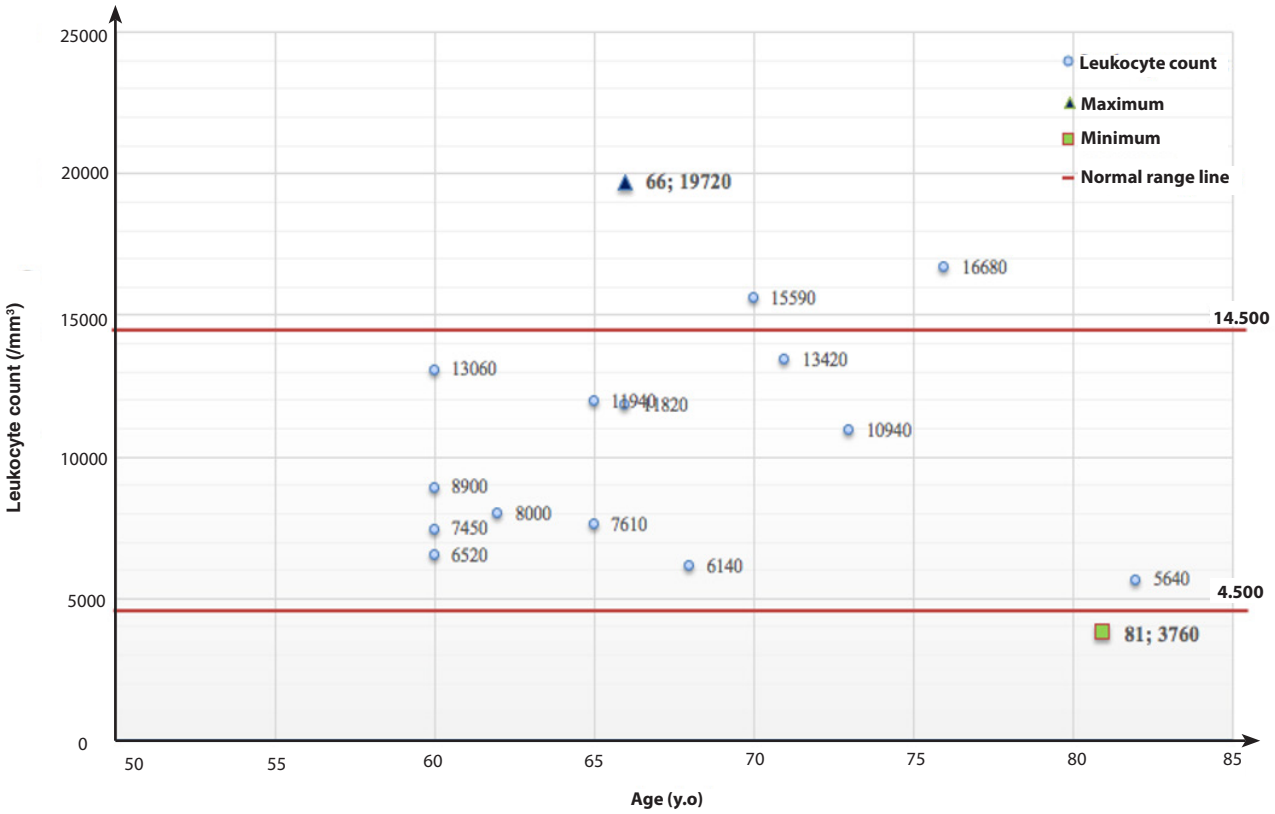

Figure 2. Scattered plot of the total leukocyte count distribution in elderly patients with a ventilator

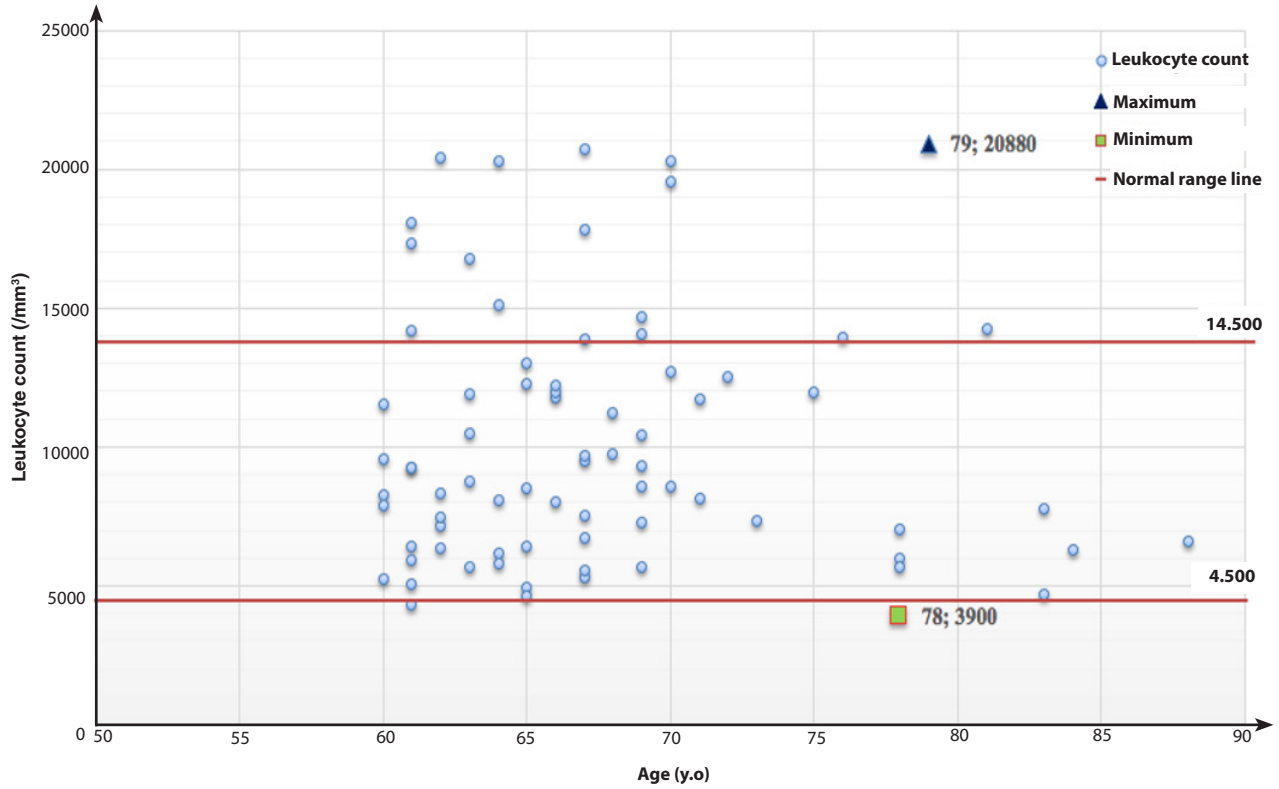

Figure 3. Scattered plot of the total leukocyte count distribution in elderly patients without a ventilator

Table 3. The prevalence of elderly patients confirmed COVID-19 with vs without a ventilator based on gender, age, and total leukocyte count in 2021

Characteristics		Patients with a ventilator	Patients without a ventilator	With a ventilator vs Without a ventilator		
				Significance	OR	95% confident interval
Gender	Male	7 (13.2)	46 (86.8)	0.369*	Ref	0.640-5.775
	Female	9 (22.5)	31 (77.5)		1.923	
	Total	16 (17.2)	77 (82.8)			
Age (Years old)	**Age**	66 (60-82)	66 (60-88)	0.959**	1.001	0.922-1.086
	Productive age					
	≤64	5 (14.7)	29 (85.3)	0.842*	Ref	0.221-3.417
	>64	11 (18.6)	48 (81.4)		0.870	
	Total	16 (17.2)	77 (82.8)			
	High-risk age					
	<70	10 (14.9)	57 (85.1)	0.369*	Ref	0.385-5.824
	≥70	6 (23.1)	20 (76.9)		1.497	
	Total	16 (17.2)	77 (82.8)			
	Total leukocyte count	9.920 (3.760-19.720)	8,750 (3.900-20.880)	0.756**	1.000	1.000-1.000
	Low	1 (33.3)	2 (66.7)	1.000*	Ref	0.441-1.741
	Normal	12 (82.9)	58 (17.1)		0.876	
	High	3 (15)	17 (85)			
	Total	16 (17.2)	77 (82.8)			

**Chi-square* or fisher exact test; **Mann whitney test

DISCUSSION

This study discovered that the majority of elderly patients confirmed COVID-19 in X general hospital Surabaya in 2021 were hospitalized in the COVID-19 isolation room on the 4th floor (77 elderly patients) rather than in the COVID-19 ICU room on the 6th floor. The determinant factor that could affect this phenomenon is the COVID-19 vaccine. The COVID-19 vaccine for the elderly in Indonesia started in January 2021, earlier than the plan. Hence, at least some elderly patients involved in this study had their first dose of the COVID-19 vaccine (Arifin and Anas, 2021).

The COVID-19 vaccine is one of the ways to prevent severe outcomes of COVID-19, including in high-risk populations (Andrews *et al*., 2022; Baum *et al*., 2022; Mazagatos *et al*., 2021; Moline *et al*., 2021). Administering the COVID-19 vaccine to the elderly must be done carefully. The aging process could decrease the immune system and response of the elderly, known as immunosenescence. Besides that, the aging process decreases organ function and increases the risk of having comorbidities, including waning the vaccine's effectiveness. Due to this condition, when given vaccination, the elderly population may not have an antibody development rate as high as the adult population. The elderly who wants to get the vaccine must obtain the physician's approval to show that the elderly are eligible to get the vaccine. However, the seroconversion rate was not as high as the adult population. It actually can protect our elderly from a severe illnesses that may lead to higher hospitalization rates and death (Setiati and Jessica, 2021).

The elderly patients confirmed COVID-19 involved in this study were 93 patients. The majority of the elderly patients were male, with the age ranging from 60 to 69 years old. Based on the severity, this study revealed that female was more likely to require a ventilator treatment up to 1.9 times higher than male but not significantly different between male and female (*p-value* = 0.369). Risk factors based on gender discovered that the susceptibility to infected COVID-19 was more likely in males. Females were more likely to have positive behavior regarding the prevention of COVID-19 than males, like hand hygiene practices and seeking preventive care. In contrast, males were more likely to have high-risk behavior, such as ignoring physical distancing or smoking (Sharma *et al*., 2020).

Females have a more robust immune system than males, estrogen and the X chromosome in females play a positive role in this system. Therefore, females have stronger innate and adaptive immune responses than males. This results in faster clearance of pathogens and greater vaccine efficacy. Another biological factor difference could relate to sex differences in *Angiotensin-Converting Enzyme 2* (ACE2) receptors.

ACE2 plays a role as the gateway for the virus entry into the tissue. The density of ACE2 receptors is much higher in the testes than in the ovaries. Meanwhile, the previous study by Fernandez (2017) found out that older women above 55 had significantly higher ACE2 activity than women younger than 55 years old, with no significant difference in serum ACE2 activity between older and younger men. Further, excessive ACE2 expression will increase the severity of COVID-19 (Fernandez-Atucha *et al*., 2017; Papadopoulos *et al*., 2021; Salah and Mehta, 2021; Sharma *et al*., 2020; Vahidy *et al*., 2021).

This study presented that the majority of the leukocyte count of elderly patients confirmed COVID-19 was in the normal range. However in the elderly patient with a ventilator, we discovered that the leukocyte count was more likely above normal than below normal with the ratio 1 : 3 for low and high leukocyte counts respectively. Several studies unveiled that severe COVID-19 tended to have a higher leukocyte count, while normal leukocyte count could be discovered in mild and moderate COVID-19. Higher leukocyte count can indicate prominent developed inflammation (Anurag *et al*., 2020; Gao *et al*., 2021; Huang *et al*., 2020).

The progressive increase in leukocyte count may be associated with the progression of inflammatory status or *Systemic Inflammatory Response to various Severe* clinical insults (SIRS). SIRS is often defined by at least two parameters, including hypothermia or hyperthermia; tachycardia, tachypnea, or hypocapnia; and leukocytosis, leukopenia, or an increased number of immature leukocytes. Increasing leukocyte count was more likely to develop SIRS. In the acute phase, procalcitonin, IL-6, and CRP can be released as the biomarker of SIRS. Procalcitonin levels can be slightly higher in viral infections and significantly increase in bacterial, fungal, or parasitic infections. Whereas, IL-6 and CRP become a predictor of the severity and outcome of SIRS. COVID-19 patients with increased leukocyte count reveal the increasing concentration of procalcitonin, CRP, and IL-6 in the serum. These results indicated that the confirmed COVID-19 patients with higher leukocyte count had a significantly higher level of systemic inflammation response and at least partially related to critical illness outcome (Gao *et al*., 2021; Lohmann and Barton, 2014; Zhao *et al*., 2020).

Meanwhile, severe and critical COVID-19 could also have leukopenia followed by thrombocytopenia and lymphocytopenia, especially CD4+ T and CD8+ T, which play a significant role in mediating immune response because of the secretion of specific cytokines. Cytopenia during infection-related SIRS may result from decreased bone marrow production or increased destruction. The bone marrow cytopenia (leukopenia and thrombocytopenia) may arise due to maturation arrest, inadequate bone marrow supply of progenitors, or hemophagocytosis. These were identified as independent predictors of severe and critical COVID-19 (Belok *et al*., 2021; Luckheeram *et al*., 2012; Yongzhi, 2021).

Risk factors were identified as the progression of COVID-19 into the severe and critical stage. One of the risk factors identified in this study was older age or 70 years old and above. Older age is more likely to have comorbidities, weaker immune defense, and higher levels of pro-inflammatory cytokines (Gao *et al*., 2021; Gomez-Belda *et al*., 2021). A meta-analysis by Pijls *et al*. (2020) indicated that demographic factors such as age 70 years and above appeared to have a 65% higher risk for getting infected with COVID-19. When infected, they also had a higher risk for severe COVID-19 including the need for intensive care (Pijls *et al*., 2021).

The limitation of our study includes the data, especially comorbidity data of the patients. Additionally, this study was focusing on the elderly patients aged 60 years old and over. The elderly patients tend to have the higher risk of comorbidities. This may lead elderly patients COVID-19 to become more vulnerable and need the professional healthcare treatment.

CONCLUSION

COVID-19 patients may have low, normal or high leukocyte count. Leukocyte count may help further in following the progression of the disease and help in the decision making regarding treatment strategy to prevent the cytokine storm. Being able to prioritize patients with severe illnesses is crucial. Early diagnosis through laboratory assessment can help the susceptible patient with severe COVID-19 obtain the proper therapy.

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REFERENCE

Aminzadeh, Z., Parsa, E., 2011. Relationship between Age and Peripheral White Blood Cell Count in Patients with Sepsis. Int. J. Prev. Med. Vol. 2(4), Pp. 238-242.

Andrews, N., Tessier, E., Stowe, J., Gower, C., Kirsebom, F., Simmons, R., Gallagher, E., Thelwall, S., Groves, N., Dabrera, G., Myers, R., Campbell, C.N.J., Amirthalingam, G., Edmunds, M., Zambon, M., Brown, K., Hopkins, S., Chand, M., Ladhani, S.N., Ramsay, M., Bernal, J.L., 2022. Duration of Protection against Mild and Severe Disease by Covid-19 Vaccines. N. Engl. J. Med. Vol. 386(4), Pp. 340-350.

Anurag, A., Jha, P.K., Kumar, A., 2020. Differential White Blood Cell Count in The COVID-19: A Cross-Sectional Study of 148 Patients. Diabetes Metab. Syndr. Clin. Res. Rev. Vol. 14(6).

Arifin, B., Anas, T., 2021. Lessons Learned from COVID-19 Vaccination in Indonesia: Experiences, Challenges, and Opportunities. Hum. Vaccines Immunother. Vol. 17(11), Pp. 3898–3906.

Baum, U., Poukka, E., Leino, T., Kilpi, T., Nohynek, H., Palmu, A.A., 2022. High Vaccine Effectiveness against Severe Covid-19 in The Elderly in Finland Before and After the Emergence of Omicron. BMC Infect. Dis. Vol. 816.

Belok, S.H., Bosch, N.A., Klings, E.S., Walkey, A.J., 2021. Evaluation of Leukopenia during Sepsis as A Marker of Sepsis-Defining Organ Dysfunction. PLoS One Vol. 16(6), Pp. e0252206.

CDC, 2020. COVID-19 Risks and Vaccine Information for Older Adults.

Dhinata, K.S., 2021. Common Change of Complete Blood Count Parameters in COVID-19: a Literature Review. J. Med. Heal. Vol. 3(2), Pp. 198–207.

Fernandez-Atucha, A., Izagirre, A., Fraile-Bermudez, A.B., Kortajarena, M., Larrinaga, G., Martinez-Lage, P., Echevarría, E., Gil, J., 2017. Sex Differences in The Aging Pattern of Renin-Angiotensin System Serum Peptidases. Biol. Sex Differ. Vol. 8(1), Pp. 1-8.

Ganie, M.S.F., 2020. Hubungan COVID-19 terhadap Masyarakat Lanjut Usia. J. Med. Hutama Vol. 3(1), Pp. 1304–1308.

Gao, Y.-D., Ding, M., Dong, X., Zhang, J.-J., Azkur, A.K., Azkur, D., Gan, H., Sun, Y.-L., Fu, W., Li, W., Liang, H.-L., Cao, Y.-Y., Yan, Q., Cao, C., Gao, H.-Y., Bruggen, M.-C., Veen, W. van de, Sokolowska, M., Akdis, Mu., Akdis, C.A., 2021. Risk Factors for Severe and Critically ill COVID-19 Patients: A Review. Allergy Vol. 76(2), Pp. 428-455.

Gomez-Belda, A.B., Fernandez-Garces, M., Mateo-Sanchis, E., Madrazo, M., Carmona, M., Piles-Roger, L., Artero, A., 2021. COVID-19 in Older Adults: What are The Differences with Younger Patients? Geriatr. Gerontol. Int. Vol. 2(1), Pp.60–65.

Huang, G., Kovalic, A.J., Graber, C.J., 2020. Prognostic Value of Leukocytosis and Lymphopenia for Coronavirus Disease Severity. Emerg. Infect. Dis. Vol. 26(8), Pp. 1839–1841.

Lohmann, K.L., Barton, M.H., 2014. Chapter 11 - Systemic Inflammatory Response Syndrome. Equine Infect. Dis. Second Ed. Pp. 119-131.

Luckheeram, R.V., Zhou, R., Verma, A.D., Xia, B., 2012. CD4 +T cells: Differentiation and functions. Clin. Dev. Immunol.

Mazagatos, C., Monge, S., Olmedo, C., Vega, L., Gallego, P., Martin-Merino, E., Sierra, M.J., Limia, A., Larrauri, A., 2021. Effectiveness of mRNA COVID-19 Vaccines in Preventing SARS-CoV-2 Infections and COVID-19 Hospitalisations and Deaths in Elderly Long-Term Care Facility Residents, Spain, weeks 53 2020 to 13 2021. Eurosurveillance Vol. 26(24), Pp. 1-6.

Ministry of Health Indonesia, 2020. Keputusan Menteri Kesehatan Republik Indonesia Nomor HK.01.07/ MenKes/413/2020 Tentang Pedoman Pencegahan dan Pengendalian Corona Virus Disease 2019 (Covid-19), MenKes/413/2020.

Ministry of Health Indonesia, 2021. Profil Kesehatan Indonesia 2020.

Moline, H.L., Whitaker, M., Deng, L., Rhodes, J.C., Milucky, J., Pham, H., Pate, K., Anglin, O., Reingold, A., Chai, S.J., Alden, N.B., Kawasaki, B., Meek, J., Yousey-Hindes, K., Anderson, E.J., Farley, M.M., Ryan, P.A., Kim, S., Nunez, V.T., Como-Sabetti, K., Lynfield, R., Sosin, D.M., McMullen, C., Muse, A., Barney, G., Bennett, N.M., Bushey, S., Shiltz, J., Sutton, M., Abdullah, N., Talbot, H.K., Schaffner, W., Chatelain, R., Ortega, J., Murthy, B.P., Zell, E., Schrag, S.J., Taylor, C., Shang, N., Verani, J.R., Havers, F.P., 2021. Effectiveness of COVID-19 Vaccines in Preventing Hospitalization among Adults Aged >65 Years — COVID-NET. MMWR Recomm. Reports Vol. 70(32), Pp. 1088-1093.

Papadopoulos, V., Li, L., Samplaski, M., 2021. Why Does COVID-19 Kill more Elderly Men Than Women? Is There a Role for Testosterone? Andrology Vol. 9(1), Pp. 65-72.

Pijls, B.G., Jolani, S., Atherley, A., Derckx, R.T., Dijkstra, J.I.R., Franssen, G.H.L., Hendriks, S., Richters, A., Venemans-Jellema, A., Zalpuri, S., Zeegers, M.P., 2021. Demographic Risk Factors for COVID-19 Infection, Severity, ICU Admission and Death: A Meta-Analysis of 59 Studies. BMJ Open Vol. 11(1), Pp. 1-10.

Salah, H.M., Mehta, J.L., 2021. Hypothesis: Sex-Related Differences in ACE2 Activity May Contribute to Higher Mortality in Men Versus Women with COVID-19. J. Cardiovasc. Pharmacol. Ther. Vol. 26(2), Pp. 114-118.

Satgas COVID-19, 2022. Data Sebaran. Indonesia.

Selim, S., 2020. Leukocyte Count in COVID-19: An Important Consideration. Egypt. J. Bronchol. Vol. 43.

Setiati, S., Jessica, M., 2021. COVID-19 Vaccine for Elderly: Should We be Reactive or Proactive? Acta Med. Indones. Vol. 53(1), Pp. 1-4.

Sharma, G., Volgman, A.S., Michos, E.D., 2020. Sex Differences in Mortality from COVID-19 Pandemic. JACC Case Reports Vol. 2(9), Pp. 1407–1410.

Vahidy, F.S., Pan, A.P., Ahnstedt, H., Munshi, Y., Choi, H.A.Y.T., Nasir, K., Kash, B.A., Andrieni, J.D., McCullough, L.D., Lazzeri, C., 2021. Sex Differences in Dusceptibility, Deverity, and Outcomes of Coronavirus Disease 2019: Cross-Sectional Analysis from A Diverse US Metropolitan Area. PLoS One Vol. 16(1), Pp. e0245556.

WHO, 2021. Coronavirus Disease 2019 (COVID-19) Situation Report-60. COVID 19. URL https://cdn.who.int/media/docs/default-source/searo/indonesia/covid19/external-situation-report-46_10-march-2021-update.pdf?sfvrsn=1859ffc2_5

WHO, 2020. Naming The Coronavirus Disease (COVID-19) and The Virus that Causes It.

Yongzhi, X., 2021. COVID-19-Associated Cytokine Storm Syndrome and Diagnostic Principles: An Old and New Issue. Emerg. Microbes Infect. Vol. 10(1), Pp. 266–276.

Zhao, K., Li, R., Wu, X., Zhao, Y., Wang, A., Zheng, Z., Zeng, S., Ding, X., Nie, H., 2020. Clinical Features in 52 Patients with COVID-19 who Have Increased Leukocyte Count: A Retrospective Analysis. J. Clin. Microbiol. Infect. Dis. Vol. 39(12), Pp. 2279-2287.

Zhu, B., Feng, X., Jiang, C., Mi, S., Yang, L., Zhao, Z., Zhang, Y., Zhang, L., 2021. Correlation between White Blood Cell Count at Admission and Mortality in COVID-19 Patients: A Eetrospective Study. BMC Infect. Dis. Vol. 21(1), Pp. 1-5.