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DAFTAR ISI

Artikel Penelitian

Tinjauan Pustaka

Correlation Between Leukocyte Differential Counts with The Severity and Outcome of Coronavirus Disease 2019 (Covid-19) Patients in Jember

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Abstract

Background: *Coronavirus Disease 2019 (Covid-19) is an acute respiratory disease caused by a new strain of RNA viruses named Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2). Hematological changes, especially leukocyte differential counts, are presumed to be a predictor of the severity and outcome of Covid-19 patients. This study aimed to analyze the correlation between leukocyte differential counts with the severity and outcome of Covid-19 patients.*

Methods: *This study was conducted using a cross-sectional analytic observational method, through secondary data analysis of Covid-19 patients who were tested positive by Reverse Transcriptase-Polymerase Chain Reaction (RT-PCR) and hospitalized between April–November 2020 at Citra Husada Jember, Kaliwates Jember, and Jember Klinik Hospital.*

Results: *From 267 patients, there were 139 female patients (52.1%) and 128 male patients (47.9%). There was a positive correlation on leukocytes, neutrophils, and neutrophil-lymphocyte ratio (NLR) with the severity and outcome of the patients and a negative correlation on eosinophils, lymphocytes, and monocytes (P<0.001). Basophil had a positive correlation with patient severity (P<0.05), but no significant correlation with patient outcome (P>0.05)*

Conclusion: *Leukocyte differential counts examination could be a predictor of the severity and outcome of Covid-19 patients, especially neutrophils, lymphocytes, and NLR.* ***(J Respirol Indones 2021; 41(3): 187–95)***

Keywords: *Covid-19, leukocyte differential counts, outcome, severity.*

Hubungan Gambaran Hitung Jenis Leukosit dengan Tingkat Keparahan dan Luaran Pasien *Coronavirus Disease 2019* (Covid-19) di Jember

Abstrak

Latar Belakang: *Coronavirus Disease 2019 (Covid-19) merupakan penyakit pernapasan akut akibat virus RNA* strain *baru yaitu* Severe *Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2). Perubahan hematologi, khususnya hitung jenis leukosit, diduga dapat menjadi prediktor tingkat keparahan serta luaran pasien Covid-19. Tujuan penelitian ini adalah untuk menganalisis hubungan gambaran hitung jenis leukosit dengan tingkat keparahan dan luaran pasien terkonfirmasi Covid-19.*

Metode: *Penelitian menggunakan metode observasional analitik potong lintang melalui analisis data sekunder pada pasien terkonfirmasi Covid-19 yang dibuktikan dengan pemeriksaan Reverse Transcriptase-Polymerase Chain Reaction (RT-PCR) dan dirawat inap antara bulan April–November 2020 di Rumah Sakit Citra Husada Jember, Kaliwates Jember, dan Jember Klinik.*

Hasil: *Dari 267 pasien, didapatkan 139 pasien perempuan (52.1%) dan 128 pasien laki-laki (47,9%). Terdapat korelasi positif pada jumlah leukosit, kadar neutrofil, dan rasio neutrofil-limfosit (NLR) dengan tingkat keparahan dan luaran pasien, serta korelasi negatif pada kadar eosinofil, limfosit, dan monosit (P<0,001). Kadar basofil memiliki korelasi positif dengan tingkat keparahan pasien (P<0,05), namun tidak memiliki korelasi yang bermakna terhadap luaran pasien (P>0,05)*

Kesimpulan: *Pemeriksaan hitung jenis leukosit dapat menjadi prediktor tingkat keparahan dan luaran pasien Covid-19, khususnya neutrofil, limfosit, dan NLR.* ***(J Respirol Indones 2021; 41(3): 187–95)***

Kata Kunci: *Covid-19, hitung jenis leukosit, luaran, tingkat keparahan.*

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INTRODUCTION

Coronavirus Disease 2019 (Covid-19) is an acute respiratory disease caused by a single-stranded RNA virus that has a sheath, namely Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). SARS-CoV-2 belongs to the genus *Betacoronavirus* and subgenus *Sarbecovirus,* which was first discovered in early January 2020 as the time when there was an outbreak of pneumonia in Wuhan, China, at the end of December 2019.[1]

The spread of SARS-CoV-2 is very massive compared to other coronaviruses, namely Middle-East Respiratory Syndrome Coronavirus (MERS-CoV) and Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV). SARS-CoV first appeared in 2002 in Guangdong, China, with more than 8,000 confirmed cases, while MERS-CoV first appeared in 2012 in Saudi Arabia with 2,494 positive cases.[2] Based on global data on June 23rd, 2020, the number of confirmed Covid-19 cases reached 8,974,795 patients.[3] Meanwhile, in Indonesia, cases of confirmed COVID-19 reached 47,896 patients,[4] including in Jember Regency of 104 patients.[5]

The 5th revision of Covid-19 Control and Prevention Guidelines from the Ministry of Health Republic of Indonesia divides the criteria for the severity of Covid-19 patients into five groups, namely asymptomatic, mild, moderate, severe, and critical. In the mild group, patients have general non-specific symptoms, such as cough, fever, sore throat. The moderate group have signs of mild pneumonia. The severe ones have RR >30x/minute and/or SpO_2<90% while the critical patients have symptoms that develop into Acute Respiratory Distress Syndrome (ARDS). On the final evaluation of the patient's clinical status, the patient is declared cured if once confirmed, have met the criteria for completion of isolation, added with a statement letter of monitoring completion based on an assessment by the doctor at the health service facility.[6]

Transmission of SARS-CoV-2 from human to human can be through direct or indirect contact in the form of droplets from an infected person which enters the respiratory tract.[7] SARS-CoV-2 will infect host cells through the spike protein binding with Angiotensin-Converting Enzyme receptors-*2* (ACE-2).[8]

The body will produce an immune response via proinflammatory cytokines and chemokines, namely IL-1β, IL-6, IL-8, IL-12, and TNF-α, as well as late production of IFN-1 through macrophages. Uncontrolled production of proinflammatory cytokines due to persistent and worsening infections will cause cytokine storm which leads to worsening of the severity and outcome of Covid-19 patients.[9]

The gold-standard examination for SARS-CoV-2 infection is the nucleic acid test through real-time reverse transcription-polymerase chain reaction (RT-PCR).[3] In addition to the RT-PCR examination, there are supporting tests that are useful to evaluate the characteristics of Covid-19 patients, one of which is the leukocyte count. Leukocytes are divided into two groups, namely granulocytes (neutrophils, basophils and eosinophils) and agranulocytes (monocytes and lymphocytes). Leukocytes are thought to have contributed to the cytokine storm in Covid-19 patients, which resulted in the worsening of the patient's condition in ARDS.[10]

A study of 99 patients with confirmed Covid-19 in Wuhan, China, 24 patients (24%) experienced an increment in the number of leukocytes, neutrophils increased in 38 patients (38%) and lymphocytes decreased in 35 patients (35%).[11] In Covid-19 patients who died, the number of neutrophils continued to escalate and the number of lymphocytes continued to decline until death.[12]

The purpose of this study was to analyze the correlation between the type of leukocyte count and the severity and outcome of Covid-19 confirmed patients. The results of this study were expected to be able to identify Covid-19 patients with a high risk of poor prognosis and death so that appropriate treatment could be carried out.

METHOD

This study used a cross-sectional analytic observational method through secondary data analysis from medical records. The study sample was taken using a total population sampling and acquired 492 patient data. About 267 data met the inclusion criteria, namely patients who were confirmed positive for Covid-19 by RT-PCR and hospitalized between April to November 2020 at Covid-19 referral hospital in Jember Regency (Citra Husada Jember Hospital, Kaliwates Jember Hospital and Jember Clinic Hospital). The study exclusion criteria were patients with unclear outcomes such as being referred to another hospital during hospitalization or discharge on patient's request and incomplete medical records.

Patient severity was classified into mild, moderate, severe, and critical. Patient outcomes were divided into recovered and died. Meanwhile, the leukocyte count were grouped into decreased, normal, and increased categories, adjusted to the normal values of the laboratory for each hospital. The correlation test of categorical data on each type of leukocyte count with the severity and outcome of patients with confirmed Covid-19 was performed using the Spearman test by SPSS version 23.

RESULT

In this study, of the 267 patients with confirmed Covid-19, about 47.9% were male and 52.1% were female. The mean age was 44.44±0.96 years (95% CI=42.6–46.45), with the largest age group being 41–60 years (44.6%), followed by 21–40 years (34.8%), >60 years (15%), and <21 years (5.6%). About 63.7% of patients did not have comorbidities, while the rest 36.3% had at least one comorbid disease. The level of education in most patients was D3/D4/S1/equivalent (43.1%) and high school graduates (37.5%). Most of the patients were office workers (50.2%), unemployed (16.9%), housewives (16.1%), and medical personnel (6.4%). The general characteristics of the study sample can be seen in Table 1.

The correlation between leukocyte count and the severity of Covid-19 patients can be seen in Table 2. There were positive correlation with weak correlation strength in leukocytes (r = 0.283; *P*<0.001), neutrophils (r = 0.360; *P*<0.001) and NLR. (r = 0.374; *P*<0.001), positive correlation with very weak correlation strength for basophils (r = 0.159; *P*<0.05), and negative correlation with weak correlation strength for eosinophils (r = -0.214; *P*<0.001), lymphocytes (r = -0.397; *P*<0.001) and monocytes (r = -0.290; *P*<0.001).

The leukocyte count tended to be normal in all groups of Covid-19 patients, but when compared with severe and critical groups, more patients experienced an increase in leukocytes compared to mild and moderate groups (52.4%; 36.4% vs 5.4%; 11.5%). Neutrophils and NLR in severe and critical groups were also found to have elevated more (81%; 90.9% and 71.4%; 81.8%) while lymphocytes in severe and critical patients were found to have declined more (66.7%; 72.7 %).

Table 1. The general characteristics of patients (n=267) with confirmed Covid-19

Variable	n (%)[a]
Gender	
Male	128 (47.9%)
Female	139 (52.1%)
Age, average (year)[2]	44.44±0.96 (95% CI 42.6-46.45)
Age' Classification	
<21 year	15 (5.6%)
21-40 year	93 (34.8%)
41-60 year	119 (44.6%)
> 60 years	40 (15.0%)
Comorbid classification	
Non-Comorbid	170 (63.7%)
Comorbid	97 (36.3%)
Level of education	
No School	12 (4.5%)
Elementary School	27 (10.1%)
Junior High School	13 (4.9%)
Senior High School	100 (37.5%)
D3/D4/S1/equivalent	115 (43.1%)
Profession	
Not Working	45 (16.9%)
Housewife	43 (16.1%)
Medical Personnel	17 (6.4%)
Military/police	6 (2.2%)
Office worker	134 (50.2%)
Farmer	7 (2.6%)
Etc	15 (5.6%)

Note: [a]n (%) = total and percentage of each characteristic;
[b]Age, average (year) = *mean ± standard error (95% CI)*

Table 2. Correlation of leukocytes count and the severity of patients with confirmed COVID-19

Variable		Severity				Score
		Mild (n=93)	Moderate (n=131)	Severe (n=21)	Critical (n=22)	
Leukocyte	Decreased	4 (4.3%)	2 (1.5%)	1 (4.8%)	1 (4.5%)	r = 0.283 *P*= 0.0001
	Normal	84 (90.3%)	114 (87.0%)	9 (42.9%)	13 (59.1%)	
	Increase	5 (5.4%)	15 (11.5%)	11 (52.4%)	8 (36.4%)	
Neutrophils	Decreased	6 (7.1%)	6 (4.7%)	0 (0.0%)	0 (0.0%)	r = 0.360 *P* = 0.0001
	Normal	55 (64.7%)	62 (48.1%)	4 (19.0%)	2 (9.1%)	
	Increase	24 (28.2%)	61 (47.3%)	17 (81.0%)	20 (90.9%)	
Eosinophils	Decreased	44 (47.3%)	89 (67.9%)	15 (71.4%)	15 (68.2%)	r = -0.214 *P* = 0.0001
	Normal	36 (38.7%)	36 (27.5%)	6 (28.6%)	7 (31.8%)	
	Increase	13 (14.0%)	6 (4.6%)	0 (0.0%)	0 (0.0%)	
Basophils	Decreased	62 (66.7%)	89 (67.9%)	11 (52.4%)	5 (22.7%)	r = 0.159 *P* = 0.009
	Normal	31 (33.3%)	41 (31.3%)	10 (47.6%)	17 (77.3%)	
	Increase	0 (0.0%)	1 (0.8%)	0 (0.0%)	0 (0.0%)	
Limfosit	Decreased	13 (14.0%)	37 (28.2%)	14 (66.7%)	16 (72.7%)	r = -0.397 *P* = 0.0001
	Normal	67 (72.0%)	89 (67.9%)	7 (33.3%)	6 (27.3%)	
	Increase	13 (14.0%)	5 (3.8%)	0 (0.0%)	0 (0.0%)	
Monosit	Decreased	11 (11.8%)	30 (22.9%)	6 (28.6%)	16 (72.7%)	r = -0.290 *P* = 0.0001
	Normal	67 (72.0%)	88 (67.2%)	15 (71.4%)	4 (18.2%)	
	Increase	15 (16.1%)	13 (9.9%)	0 (0.0%)	2 (9.1%)	
NLR	Decreased	9 (9.7%)	7 (5.3%)	0 (0.0%)	0 (0.0%)	r = 0.374 *P* = 0.0001
	Normal	67 (72.0%)	80 (61.1%)	6 (28.6%)	4 (18.2%)	
	Increase	17 (18.3%)	44 (33.6%)	15 (71.4%)	18 (81.8%)	

Table 3. Correlation between leukocytes count and the outcome of patients with confirmed COVID-19

Variable		Outcome		Score
		Recovered (n=239)	Died (n=28)	
Leukocyte	Decreased	7 (2.9%)	1 (3.6%)	r = 0.272 *P* = 0.0001
	Normal	206 (86.2%)	14 (50.0%)	
	Increase	26 (10.9%)	13 (46.4%)	
Neutrophils	Decreased	13 (5.4%)	0 (0.0%)	r = 0.237 *P* = 0.0001
	Normal	122 (51.0%)	5 (17.9%)	
	Increase	104 (43.5%)	23 (82.1%)	
Eosinophils	Decreased	141 (59.0%)	22 (78.6%)	r = -0.131 *P* = 0.032
	Normal	79 (33.1%)	6 (21.4%)	
	Increase	19 (7.9%)	0 (0.0%)	
Basophils	Decreased	152 (63.6%)	15 (53.6%)	r = 0.062 *P* = 0.311
	Normal	86 (36.0%)	13 (46.4%)	
	Increase	1 (0.4%)	0 (0.0%)	
Limfosit	Decreased	64 (26.8%)	16 (57.1%)	r = -0.210 *P* = 0.001
	Normal	157 (65.7%)	12 (42.9%)	
	Increase	18 (7.5%)	0 (0.0%)	
Monosit	Decreased	50 (20.9%)	13 (46.4%)	r = -0.146 *P* = 0.017
	Normal	162 (67.8%)	12 (42.9%)	
	Increase	27 (11.3%)	3 (10.7%)	
NLR	Decreased	16 (6.7%)	0 (0.0%)	r = 0.236 *P* = 0.0001
	Normal	148 (61.9%)	9 (32.1%)	
	Increase	75 (31.4%)	19 (67.9%)	

Eosinophils tended to be lower in patients with mild symptoms (47.3%), moderate (67.9%), severe (71.4%), and critical (68.2%). In basophil levels, mild, moderate, and severe patients experienced a reduction (66.7%; 67.9%; 52.4%). However, more critical patients had normal basophil levels (77.3%). Meanwhile, more acute patients experienced a decrease in monocytes levels (72.7%).

The correlation between leukocyte count and the outcome of COVID-19 patients can be seen in Table 3. There were positive correlation with weak correlation strength between leukocytes (r = 0.272; *P*<0.001), neutrophils (r = 0.237; *P*<0.001), and NLR (r = 0.236; *P*<0.001), negative correlation with weak correlation strength in lymphocytes (r = -0.210; *P*<0.05) and negative correlation with very weak correlation strength for eosinophils (r = -0.131; *P*<0.05) and monocytes (r = -0.146; *P*<0.05).

Meanwhile, basophil levels did not have a significant correlation with the outcome of Covid-19 patients (r=0.062; *P*>0.05). Patients who were declared cured and died tended to have normal leukocyte counts (86.2% and 50%). Patients with mortality outcomes were also found to have elevated levels of neutrophils and NLR (82.1%; 67.9%). This contrasted with eosinophils, lymphocytes and monocytes that were found to decline more (78.6%; 57.1%; 46.4%) in patients with mortality outcomes.

DISCUSSION

Among the sample of 267 confirmed patients, Covid-19 were found to be more common in women than men. Nonetheless, they did not differ significantly (52.1% vs 47.9%). The mean age of the patients was 44.44±0.96 years (95% CI=42.6–46.45) with the 41-60 years age group as the most prevalent (44.6%). Most of the patients had at least one comorbid disease, worked as office workers (50.2%) and medical personnel (6.4%).[13]

A similar study conducted by Guan in 2020 showed that the mean age of Covid-19 patients was 47 years (35–58 years), with 41.9% of the total patients being female, 27.3% of patients had comorbid diseases, and 3.5% of patients were medical personnel. Guan explained that patients in the severe group tended to be older with a mean age of 52 years (40–60 years) and had comorbid diseases (38.7% vs 21.0%).[13]

The results of secondary data analysis showed that patients in the severe group had an escalated number of leukocytes compared to the mild and moderate groups (52.4% vs. 5.4% and 11.5%; *P*<0.001). However, this increase was not in line with the critical group, which was only 36.4%. Leukocytes that were increased in severe patients would then decrease to normal in critical patients, presumably due to persistent hyperinflammatory response as a consequence of cytokine storms that triggered an immunoparalysis state which was predisposed to secondary infection and resulted in multiple organ failure. This was characterized by a decline in lymphocytes and the function of monocytes/macrophages so that they were unable to produce IFN-γ, which played a role in cleaning infected cells to prevent sepsis.[14]

The percentage of neutrophil levels in COVID-19 patients was significantly increased in patients in the critical group than in the mild group (28.2% vs 90.9%; *P*<0.001). As with neutrophils, the neutrophil-lymphocyte ratio (NLR) of Covid-19 patients was also significantly increased in critically ill patients (18.3% vs 81.8%; *P*<0.001). This increment occurred in contrast to the eosinophil and lymphocyte levels of COVID-19 patients. Our study found significantly more eosinopenia and lymphopenia in the critical group than in the mild group ([47.3% vs. 68.2%; *P*<0.001]; [14% vs. 72.7%; *P*<0.001]).

This study was identical to a study conducted by Wang in 2020, which stated that leukocytes, neutrophils, and NLR of Covid-19 patients were significantly elevated in the severe group than in the moderate group (*P*<0.05) while lymphocytes and eosinophils declined significantly in the severe group compared to the moderate group (*P*<0.05).[15] Study conducted by Magdalena in 2021 also revealed a similar description. Patients with severe symptoms tended to experience leukocytosis (*P*=0.002; OR=0.636), neutrophilia (*P*<0.001; OR: 17.43) and lymphopenia (*P*<0.001; OR=50.21).[16]

Increased leukocytes and neutrophils are thought to be associated with persistent and worsening infection resulting in bone marrow hyperplasia compensating for the production of more granulocytes.[15] Pro-inflammatory cytokines play a role in stimulating neutrophil activation. When

the body experiences a persistent infection, neutrophils are overproduced and result in a cytokine storm event. At the same time, the decrease in lymphocytes in severe and critical patients is thought to be due to cytokine storm that accounts for lymphocyte apoptosis and atrophy of lymphoid organs, thereby inhibiting lymphocyte cell regeneration.[17]

The neutrophil-lymphocyte ratio (NLR) of Covid-19 patients in a similar study also discovered that severe patients had a higher NLR than the mild group (95% CI=0.72–1.04). In infectious diseases, NLR acts as an indicator of systemic inflammation which helps determine a patient's prognosis and outcome.[18] The decrease in eosinophils in this study was not yet known for certain regarding the role of eosinophils in SARS-CoV-2 infection. In infectious diseases, granular proteins derived from eosinophils exhibit antiviral properties against single-stranded RNA viruses. Cryptogenic eosinophils that occur in Covid-19 patients are thought to be a consequence of eosinophil secretion by the inhibited bone marrow, blockade of eosinophils, and delayed IFN-1 response resulting in eosinophil apoptosis.[19] During a cytokine storm, increased neutrophil levels lead to increased infiltration of neutrophil cells into lung tissue. This is believed to accelerate the production of neutrophils in the bone marrow, thereby suppressing eosinophil production.[20]

The correlation between basophil levels and the severity experienced by Covid-19 patients in this study had a weak correlation strength (r = 0.159). Meanwhile, in a survey conducted by Anurag in 2020, it was explained that basophil levels were not significantly associated with the severity of Covid-19 patients (*P*=0.166).[21] Like eosinophils, the role of basophils in SARS-CoV-2 infection was also not known with certainty and allegedly multifactorial. Basophils are thought to play a role in binding antigens and strengthening the humoral immune response so that the decrease in basophils during the acute phase can affect the effectiveness of IgG response against SARS-CoV-2.[22]

Significant reductions in basophils and eosinophils occurred in the majority of Covid-19 patients in the early stage or acute onset, regardless of the severity.[20] However, the decline in eosinophil and basophil levels was more serious in severe patients. In this study, more severe patients experienced a decrease in eosinophils and basophils than critical patients (71.4% vs 68.2% and 52.4% vs 22.7%); this might be due to some essential patients of this study were already in poor condition by the time of initial hospital admission or had passed the acute onset.

The monocyte levels of Covid-19 patients in this study were significantly negatively correlated in patients from the critical group compared to the mild, moderate, and severe groups (72.7% vs 11.8%; 22.9%; 28.6%; *P*<0.05). However, this phenomenon was not similar to a study from Pence in 2020, which pointed out a significant increase in monocytes that play a role in producing IL-6 in mild patients and continued to increase in severe patients.[23] Study of 32 Covid-19 patients with various severity levels and 18 healthy people as controls showed that $CD16^-$ monocyte count reduced significantly in critical patients compared to mild and severe groups (*P*<0.01). In contrast, pro-inflammatory $CD16^+$ monocytes were elevated compared to healthy controls (*P*<0.05). The study also stated that IL-6 levels had a positive correlation with the $CD16^+$ monocyte count.[24]

Monocyte $CD16^-$/classic subset, which plays a role in phagocytosis, has been significantly declined in critically ill patients, presumably due to impaired phagocytosis function because of innate immune function suppression. The results of the analysis for monocyte levels in this study were not like those of the study from Pence because they had limitations only to examine monocyte levels as a whole so that they could not identify the subset of monocyte that had lowered.

In the outcome of Covid-19 patients, the percentage of increased leukocytes was higher in patients who died (10.9% vs 46.4%; *P*<0001). Neutrophil and NLR levels were also higher in patients who died (82.1% and 67.9%; *P*<0001). At the same time, the lymphocyte levels declined more in patients who died (26.8% vs 57.1%; *P*<0.05). This

was identical to a study conducted by Zhao in 2020 which stated that the leukocyte types examination results of Covid-19 patients who died had a higher number of leukocytes ($7.85x10^9$/L vs $5.07x10^9$/L), higher neutrophil levels ($6.41x10^9$/L vs $3.08x10^9$/L), and lower lymphocyte levels ($0.69x10^9$/L vs $1.20x10^9$/L).[10] The NLR increase was also same as a study from Mousavi in 2020, which indicated that the deceased patient has a higher NLR (*P*<0,001).[25]

In this study, eosinophil levels in Covid-19 patients had a very weak negative correlation (r = -0.131; *P*<0.05) as seen in patients who recovered or died experienced a decline in eosinophils (59% and 78.6%). However, normal eosinophil levels were more common in cured patients who recovered (33.1% vs 21.4%; *P*<0.05). A corresponding study from Nair in 2020 found that eosinophil levels were negatively correlated with ICU duration, mechanical ventilation requirements, and oxygen supplementation (r = -0.34, -0.614 and -0.39; respectively, *P*<0.01).[26] A similar study suggested that eosinopenia could be a poor prognosis of Covid-19 patients outcome. Eosinophil levels that returned to normal during treatment were also considered as an indicator of clinical improvement. Nevertheless, there were no analysis of the leukocyte counts development of Covid-19 patients in this study.

Basophil levels on the outcome of Covid-19 patients in this study did not have a significant correlation (*P*=0.311), Same result was also discovered by Asghar in 2020, showing that basophil levels did not have a significant association with the outcome of Covid-19 patients (*P*=0.101).[27] Basophils do not have a significant correlation with the outcome of Covid-19 patients because most likely basophils do not have a direct contribution to cytokine storm in Covid-19 patients but instead play a role in mediating plasma B cells in response to IgG against SARS-CoV-2 infections, thus being decreased in most Covid-19 patients at acute onset.[28]

Complications from SARS-CoV-2 infection, Acute Respiratory Distress Syndrome (ARDS) are the leading cause of death for Covid-19 patients. The study has shown that cytokine storm is a mechanism for ARDS to occur in Covid-19 patients due to tissue damage.[29]

Leukocytes are thought to contribute to cytokine storms in the pathophysiology of SARS-CoV-2 infection. Cytokine storm results in the activation and infiltration of neutrophils into the alveoli, which are released by macrophages/monocytes. Injury to the alveolar epithelial cells increases the permeability of the barrier between alveolar and vascular spaces. This could bring in vascular leakage resulting in edema containing a lot of neutrophil cells and triggering the occurrence of ARDS.[30]

Lymphocytes play an important role in regulating cellular and humoral immunity. Lymphocyte levels declined more in deceased Covid-19 patients who were thought to have decreased immune function during systemic inflammatory responses. In addition, it was suspected that lymphocytes in peripheral blood vessels migrate to lung tissue during infection to eliminate the virus. This was confirmed by autopsy reports which showed that the lungs of deceased Covid-19 patients had elevated levels of lymphocytic infiltration.[31] In this study, hematologic changes in leukocytosis, neutrophilia, eosinopenia, lymphopenia, monocytopenia, and NLR increase were relevant to mortality in Covid-19 patients.

CONCLUSION

There was a significant correlation between the leukocyte count with the severity and outcome of Covid-19 confirmed patients, namely leukocytes, neutrophils, eosinophils, monocytes, lymphocytes, and NLR. Basophils, however, have a significant correlation with severity but had no significant correlation with the outcome of Covid-19 confirmed patients. Hematological examination of leukocyte counts could be a predictor of severity and outcome of Covid-19 confirmed patients, particularly the presence of neutrophilia, lymphopenia, and increased NLR.

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