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Lymphocyte Levels in Predicting the Outcome of COVID-19 Patient: A Prognostic Study from Single Center in Indonesia

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ABSTRACT

Background: Several laboratory parameters have been linked to Corona Virus Disease 2019 (COVID-19), with lymphocytes being one of the most important. Lymphopenia is frequently linked to a worsening of clinical symptoms and an increased risk of death in COVID-19. This study aimed to determine the role of lymphocyte levels in predicting COVID-19 patient mortality.

Methods: This is a prognostic study that is conducted from March 1 to August 31, 2020. Data from medical records and laboratory findings of COVID-19 patients were used in the study. Patient distribution and complete blood count were among the information gathered. ROC curve analysis, bivariate analysis (Chi-Square and Mann Whitney), in addition to survival analysis (Kaplan-Meier) were used to analyze the data.

Results: In a total of 318 patients, 59 were non-survivors and 259 were survivors. Besides, a cut-off value of ≤1460 cells/µL ($P<0.05$) was used for lymphocyte levels. Lymphopenia also has a 4.35-fold increase in the risk of mortality. Furthermore, the survival analysis revealed differences in the probability of survival within 30 days between COVID-19 patients with lymphopenia and those without (HR: 5.5722 (3.2509–9.5510), 95% CI; $p<0.0001$). A lymphocyte count of ≤1460 cell/µL can increase the risk of death by fourfold.

Conclusions: The findings of this study indicated a significant difference in outcome between lymphopenia and non-lymphopenia patients. Lymphopenia plays an important role in estimating COVID-19 patient mortality.

Keywords: COVID-19; lymphopenia; mortality; prognosis; survival analysis

INTRODUCTION

Coronavirus disease 2019 (COVID-19) is a newly emerging disease caused by Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2).[1] This disease is potentially lethal because it can cause various complications including acute respiratory distress syndrome (ARDS), septic shock, and Disseminated Intravascular Coagulation.[2] These phenomena were related to the occurrence of cytokine storms, with lymphopenia as one of the hallmarks.[3,4]

Lymphopenia is evidenced to be contributed to increased mortality, the incidence of ARDS, Intensive Care Unit (ICU) needs, as well as the incidence of severe clinical symptoms.[2,5,6] Lymphopenia is responsible for about 3-fold increased risk of severe COVID-19.[7]

Globally, there are more than 120 million confirmed cases of COVID-19.[8] This condition suggests the disease's potential risk. It is critical to have a laboratory marker that is simple and inexpensive so that it can be used throughout the hospital. This research aims to determine whether lymphocyte levels can reliably predict patient outcomes.

METHODS

This prognostic study includes medical records from March 1 through August 31, 2020. The data were obtained from Mohammad Hoesin Hospital in the South Sumatera provinces, Indonesia, which is a national referral (tertiary level) hospital in the Southern part of Sumatera. This is the only hospital with specialized ICU care for COVID-19 patients in the region. This study has been approved by the Ethics Committee of Mohammad Hoesin Hospital (Number 47/kepkrsmh/2020).

The data were collected from the medical record and laboratory examination which is started at the time when

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the patient was confirmed as a COVID-19 patient based on the reverse-transcriptase polymerase chain reaction (RT-PCR) or was the closest from the confirmation result. The inclusion criteria were adult patients (18 years or older) who had adequate medical record data that are necessary for the study. Patients with inadequate medical record data, history of malignancy, and history of Systemic Lupus Erythematosus were excluded from this study.

Patient characteristics such as age, gender, comorbid history, and outcome were acquired and analyzed, as well as hematology examination results (red blood cell (RBC) count, hemoglobin, hematocrit, platelets, white blood cell (WBC) count (WBC), WBC differential count, and neutrophil-lymphocyte ratio). The confidentiality of the data collected in this study was guaranteed, and it will only be used for research purposes.

The categorical variable was presented using n or %. The numerical variable was presented as mean ± standard deviation or median (min-max) based on the normality of data distribution. The various clinical characteristics of the patients were then compared with the patient outcomes (survivor and non-survivor). Variables were analyzed as necessary using chi-square and Mann-Whitney analysis, which reported in p-value. A p-value of <0.05 was considered significant. Optimal cut-off points for the absolute lymphocyte count based on their outcome were then obtained through the receiver operating characteristics (ROC) curve analysis. The cut-off point was then used to determine the lymphopenia and non-lymphopenia status among patients. Further analysis to determine the survival function between lymphopenia and non-lymphopenia patients was then performed using Kaplan-Meier survival analysis. Then, the Hazard Ratio (HR) was calculated. All the statistical analyses for this study were performed using IBM® SPSS statistics version 26.0 and MedCalc® 19.6.3.0 software.

RESULTS

Between March 1 and August 31, 2020, we obtained 439 medical records. Three hundred and eighteen patients meet the inclusion criteria. The features of 318 COVID-19 patients were assessed (Table 1). We discovered that out of 318 patients, 259 were declared survivors, while the remaining 59 were declared non-survivors. We found out that the median age for non-survivor was much older than survivors (Median: 57 (29 – 77) years vs. 39 (19 – 82) years; p<0.05). In terms of gender, we discovered that males were more dominant in the non-survivor group (62.7% vs. 37.3%), while females were more dominant in the survivor group (41.7% vs. 58.3%). According to our findings, gender played a role in the patient's outcome (p<0.05).

Diabetes was found to be the most common comorbidity among patients, accounting for 36 (11.3%) of the 318 patients. Diabetes was also found to be far more prevalent in non-survivor patients, with 19 (32.3%) of 59 non-survivor patients having diabetes compared to 17 (6.6%) of 259 surviving patients. This finding revealed that comorbid conditions, such as diabetes, were linked to patient outcomes (p<0.05). Other comorbidities, such as chronic kidney disease, preeclampsia, and liver disease, also played a role in the patients' history.

Data regarding the hematological parameter of the patients are presented in Table 1. The median red blood count for all 318 patients was found to be $4.35x10^6$/µL. Among patients, it is shown that red blood count appeared to be lower in non-survivors than in survivors (Median: 4.09 10^6/µL vs. 4.39 10^6/µL; p<0.05). Upon further analysis, both hemoglobin and hematocrit showed a significant decrease (p<0.05) in non-survivors compared to survivors with the non-survivors having the median hemoglobin and hematocrit at 11.7 g/dL and 33%. Meanwhile, the median number of hemoglobin and hematocrit in the survivor group were at 12.6 g/dL and 37%, accordingly. Our analysis showed that the median for white blood count among 318 patients is 9.03 10^3/µL (1.88 – 44.84$x10^3$/µL). A significant increase was seen in non-survivor in comparison to survivor patients (Median: 12$x10^3$/µL vs. 8.6$x10^3$/µL; p<0.05). The differential count showed a significant increase in median among non-survivors for neutrophil (p<0.05) and a significant decrease for eosinophil, lymphocyte, and monocyte (p<0.05) as compared to the survivor group. Further analysis revealed that non-survivors had a markedly decreased absolute lymphocyte count than survivors (p<0.05), suggesting a link between ALC and outcome. The median ALC value for non-survivor patients is 1098 cells/µL, compared to 1844 cells/µL for survivors. Furthermore, when comparing non-survivor patients to survivors, the median neutrophil-lymphocyte ratio was significantly higher in non-survivor patients (p<0.05) with 8.60 (non-survivor) vs. 3.13 (survivor), respectively.

The cut-off point (Figure 1) was calculated to be 1460 cell/µL, with a sensitivity of 74.6% and a specificity of 67.6%. The area under the ROC curve was determined to be 0.75 with p<0.001.

Lymphopenia in this study was defined as the lymphocyte value below the cut-off point. Table 2 displays that out of 318 patients, 128 were recognized with lymphopenia, and

190 were diagnosed with non-lymphopenia. Forty-four (74.6%) of the 59 non-survivor patients had lymphocyte values below the cut-off point. With a prevalence ratio of 4.35, further analysis revealed a significant correlation between clinical outcomes and lymphocyte value ($p<0.05$). The value of 1460 lymphocytes per liter was found to increase the risk of mortality up to 4.25 times.

Non-survivor patients had a median lymphocyte count of 1098 cell/µL. Kaplan-Meier survival analysis for ALC (Figure 2) revealed that lymphocyte value of 1460 cell/L was a significant predictor of mortality in COVID-19 patients ($p<0.0001$) with HR calculated at 5.57 (3.25-9.55, 95% CI). The difference between non-survivors and survivors in restricted mean survival time was 7.2438 days.

Table 1. Baseline characteristics and hematology findings of covid-19 patients.

Clinical Characteristics	All Patients (318)	Outcome		P-Value
		Non-Survivor (59)	Survivor (259)	
Characteristics				
Age (Year)	45 (19 - 82)	57 (29 - 77)	39 (19 - 82)	<0.05*
Gender				
Male	145 (45.6%)	37 (62.7%)	108 (41.7%)	<0.05**
Female	173 (54.4%)	22 (37.3%)	151 (58.3%)	
Comorbid Status				
Hypertension	32 (10.1%)	13 (22%)	19 (7.3%)	<0.05**
Diabetes Mellitus	36 (11.3%)	19 (32.3%)	17 (6.6%)	<0.05**
Cardiovascular Disease	29 (9.1%)	10 (16.9%)	19 (7.3%)	<0.05**
Other Comorbid	55 (17.3%)	22 (37.3%)	33 (12.7%)	<0.05**
Hematological Findings				
Red Blood Count (Erythrocytes) (10^6/µL)	4.35 (1.42 - 6.78)	4.09 (1.91 - 6.78)	4.39 (1.42 - 6.27)	<0.05*
Hemoglobin (g/dL)	12.5 (3.9 - 36.0)	11.7 (5.6 - 16.8)	12.6 (3.9 - 36)	<0.05*
Hematocrit (%)	37 (11 - 55)	33 (18 - 53)	37 (11 - 55)	<0.05*
Platelets (10^3/µL)	277 (3 - 782)	244 (12 - 767)	278 (3 - 782)	0.195*
White Blood Count (Leukocytes) (10^3/µL)	9.03 (1.88 - 44.84)	12 (1.88 - 30.93)	8.6 (2.69 - 44,84)	<0.05*
Differential Count				
Basophils (%)	0 (0 - 2)	0 (0 - 0)	0 (0 - 2)	0.407*
Eosinophils (%)	1 (0 - 17)	0 (0 - 6)	1 (0 - 17)	<0.05*
Neutrophils (%)	72 (1.57 - 97)	84 (15 - 97)	69 (1.57 - 96)	<0.05*
Lymphocytes (%)	18 (1 - 60)	10 (1 - 56)	22 (2 - 60)	<0.05*
Monocytes (%)	7 (0 - 17)	5 (0 - 17)	7 (1 - 17)	<0.05*
Absolute Lymphocyte Count (ALC) (cell/µL)	1667.1 (219 - 6277.6)	1098 (219 - 3093)	1844 (224 - 6277)	<0.05*
Neutrophil-Lymphocyte Ratio (NLR)	3.81 (0.04 - 97)	8.6 (0.27 - 97)	3.13 (0.04 - 48)	<0.05*

**Mann-Whitney analysis, **Chi-Square analysis*

Table 2. Lymphopenia and its correlation to patient outcome

		Patient Outcome					
		Non-Survivor		Survivor		P-Value	PR
		N	%	N	%		
Lymphocyte Value	≤ Cut-off Point (1460 Cell/µL)	44	74.6%	84	32.4%	<0.05**	4.35
	> Cut-off Point (1460 Cell/µL)	15	25.4%	175	67.6%		
	Total	59	100%	259	100%		

***Chi-Square analysis*

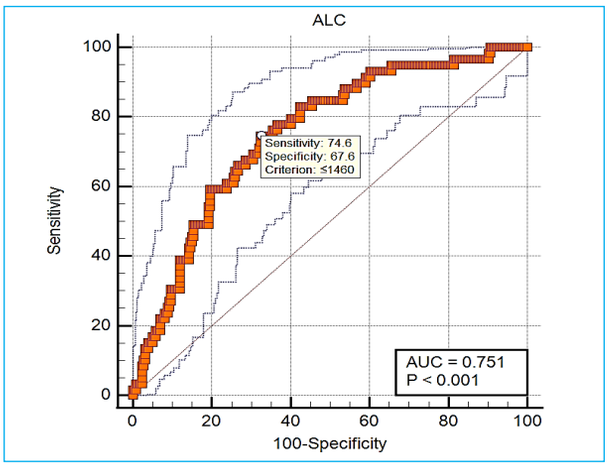

Figure 1. ROC-curve analysis for lymphocyte level.

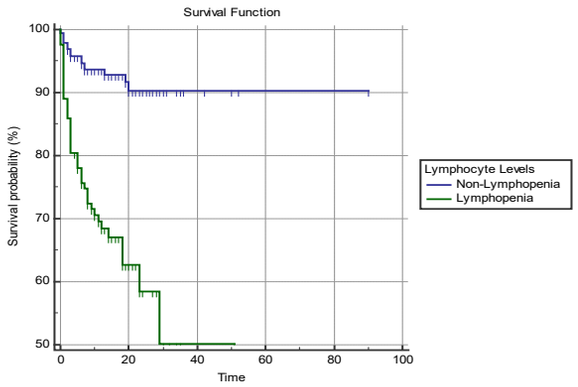

Figure 2. Kaplan-Meier survival function for lymphocyte level.

DISCUSSION

In this study, we discovered that advanced age, male gender, and a history of comorbidities were all linked to higher mortality rates, as shown in the results. This finding was similar to a previous study which found that older men had a higher mortality rate than other patients.[9,10] This was thought to be due to a weaker immune response in the elderly, which causes an increased risk of developing severe clinical symptoms and death in COVID-19 patients.[10-12] In terms of the gender effect on COVID-19, it was suggested that males had a higher risk of mortality due to lifestyle factors such as smoking, whereas females had lower susceptibility to viral infections due to the X chromosome's protection and the action of sex hormones.[10,13-15] Comorbidity history was also a key factor in COVID-19's higher death rates. In COVID-19 patients undergoing ICU treatment, there was a strong link between previous chronic illness (comorbidity) and increased mortality rates, as previously reported.[16,17]

The findings on hematological examination indicate that several markers had a strong correlation with an increased risk of death. In critical COVID-19 patients, there was a substantial decrease in hemoglobin, hematocrit, and red blood count, as reported earlier in another study.[18,19]This is thought to happen because disruption to the lungs suppresses the activities of the bone marrow, preventing the formation of important elements in the production of RBC.[18] Platelets appear to be decreasing in non-survivors compared to survivors in this study, but further statistical analysis reveals no association between platelet level and patients' outcome.

The previous report showed that leukocytosis was often found in patients with severe clinical symptoms and was associated with a poor prognosis in patients.[20,21] Similar to the earlier report, the white blood count in this study appeared to be higher. In this study, the number of eosinophils, lymphocytes, and monocytes in non-survivor patients decreased significantly, while neutrophils increased. Eosinopenia was thought to be caused by immune system fatigue in covid-19 cases. As stated in the results, we discovered that non-survivors tended to have higher NLR levels, which is linked to a poor outcome. Higher NLR was found to be significantly associated with an increased risk of mortality during hospitalization in a previous study.[22] A similar study on COVID-19 laboratory examinations found that patients with severe clinical symptoms had higher neutrophil levels and lower lymphocyte levels, which were linked to the occurrence of ARDS.[2] We found that non-survivor patients were tended to have lower macrophage levels, as also stated in the previous study.[23]leading to acute respiratory distress syndrome (ARDS Age, comorbid diseases, and environmental factors all influenced macrophage activity in SARS-CoV-2 infection.[24] In a previous study, monocyte levels in COVID-19 patients with severe clinical symptoms and diabetes mellitus comorbid were found to be lower.[25]

The value of lymphocytes was found to be crucial in predicting the outcome of COVID-19 patients in our study. Based on their lymphocyte value, there was a significant difference between non-survivor and survivor patients, as shown in the results, with lower levels in the non-survivor group. In comparison to non-lymphopenia patients, we found that lymphopenia patients had a higher risk of death and a lower overall survival rate. The non-survivor patients in our study died frequently from ARDS or multiple organ failure, and lymphopenia may have played a role in this phenomenon. The previous study also associates lymphopenia with ARDS events in COVID-19 patients.[2,26,27]

We discovered that a lymphocyte count of ≤1460 cell/μL can increase a patient's risk of death by up to fourfold, so it can be used to predict mortality in COVID-19. In a previous study, lymphocyte levels of 1500 cells/μL were known to increase the risk of serious symptomatic events by up to 3 times, while lymphocyte levels of ≤1100 cells/μL were found to have the same risk.[5,7]

Lymphopenia was thought to occur in our patients due to a variety of factors. The proposed theory of the patient's lymphopenia was caused by disease progression, which in turn increased viral load.[28,29] According to one study, viral load and lymphocyte level have a negative relationship. Severe patient lymphocyte levels and subgroups (CD8 and CD4) show a significant decrease as the disease progresses, while viral load continues to rise.[29] Comorbid factors, such as diabetes, played a role in the occurrence of lymphopenia.[30] Patients with comorbidity typically have lower organ function, which leads to a weakened immune system, which may make a contribution to lymphopenia among patients. There is also the possibility that the virus infected the immune system directly, resulting in a further drop in lymphocyte value. ACE2 expression was found on the surface of lymphocytes in the mucosa of the mouth, as well as other organs such as the digestive system and the lungs, according to one study.[31] Other studies show a possibility that the SARS-CoV-2 virus may directly destroy lymphatic organs in the body.[2,32]

Patients who did not survive were usually those who were in the most severe groups. Cytokine storms had occurred in this group, as previously stated in another section. There was an increase in pro-inflammatory cytokines during cytokine storm, which could lead to lymphocyte apoptosis.[33] Excessive cytokine activation during this phase had the potential to cause atrophy in lymphoid organs like the spleen, as well as a further reduction in lymphocytes.[2] According to the previous study, lymphocyte overactivation will be followed by a functional incidence of lymphocyte fatigue, particularly in CD8+ T cells and NK cells.[34]

Confounding factors that could cause bias in this study include the patient's comorbid diseases (hypertension, diabetes mellitus, CVD, and other comorbid), as well as the therapy and interventions provided by the patient's attending physician, are included as the limitation of this study.

CONCLUSIONS

This study showed a significant role of lymphocyte value in predicting the mortality of COVID-19 patients. A lymphocyte value of ≤1460 cells/μL could be used to predict mortality among COVID-19 patients especially those in severe subgroups.

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