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## Article

# Lymphocyte Count as Predictor of Covid-19 Patients Mortality and Length of Stay in the Covid ICU of Dr Sardjito Hospital

**[1,2]Adi Indra Wijaya*, [2]Akhmad Yun Jufan, [2]Untung Widodo**
Email (Corresponding Author) : dr.adiindra168@gmail.com*
[1] Faculty of Medicine, Universitas Ahmad Dahlan
[2] Anesthesiology and Intensive Therapy of Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada

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ABSTRACT

Covid-19 is an acute infection of the respiratory tract with a variety of clinical manifestations and severity. Lymphocyte count correlates to the severity of Covid-19. This study aims to find the relationship between lymphocyte count, mortality, and length of stay in COVID-19 patients. A retrospective cohort observational studies were conducted using medical records of confirmed COVID-19 patients in RSUP Dr. Sardjito Hospital between 1st January 2021 to 31st December 2021. The lymphocyte count cut-off point as a mortality factor was determined with the ROC curve and Youden's index. Survival analysis was done using Kaplan Meier to investigate the relation of lymphocyte count to mortality and length of stay. The correlation between lymphocyte count and other factors affecting mortality and length of stay was analyzed with Cox regression. There were 217 subjects who fulfilled the inclusion and exclusion criteria. The cut-off point of lymphocyte count was set at $1.06,10^3$ cells/µL. A total of 121 subjects have a lymphocyte count of $<1.06,10^3$ cells/µl. Higher lymphocyte counts ($\geq 1.06,10^3$ cells/µl) showed a reduced risk of mortality (HR 0.570; 95% CI 0.403 – 0.807, p=0.002). The duration of hospitalization was shorter in the group of patients with lymphocyte count $<1.06,10^3$ cells/µL OR 0.802, 95% CI 1.032-2.646; p=0.110) with a median of 128.77 hours (12.84 – 983.99 hours), which might be explained by higher mortality (p = 0.000) in the low lymphocyte patients' group (64.8%). Low lymphocytes $<1.06,10^3$ cells/µL in COVID-19 patients is independently and significantly associated with increased risk of mortality and insignificantly associated with shorter length of stay.



## INTRODUCTION

Coronavirus disease 2019 (COVID-19) is a severe acute respiratory infection disease caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), and has been declared a pandemic by World Health Organization (WHO)[1]. Where for cases in Indonesia until March 15 2022 the number of cases was 5,914,532 people with 152,745 people who died with a case fatality rate (CFR) of 2.58%[2].

Symptoms of COVID-19 vary in severity and clinical manifestations[3]. While most patients with COVID-19 have a mild influenza-like illness and may be asymptomatic, a minority of patients will experience severe pneumonia, acute respiratory distress syndrome (ARDS), multi-organ failure (MOF), and death[4]. Among those who are hospitalized, up to a quarter require ICU care.[5] Studies in 2020, concluded that the mortality rate for severe COVID-19 reaches 38% with an average length of ICU stay to death of 7 days and geriatric patients (> 65 years) with comorbidities and ARDS have an increased risk of death[6]. Based on previous research, comorbidities associated with COVID-19 outcomes include cardiovascular disease, diabetes mellitus (DM), hypertension, asthma, chronic obstructive pulmonary disease (COPD), and chronic kidney disease (CKD)[7–10].

In SARS-CoV-2 infection, it was reported that there was a decrease in the levels of T lymphocytes, B lymphocytes and natural killer (NK) cells. The decrease in the number and increase in the activity of the existing lymphocytes is positively associated with the severity of COVID-19. Decreased levels of T lymphocytes, both T CD4+ and CD8+, mainly occur in cases of COVID-19 who experience acute respiratory distress syndrome (ARDS)[11]. Laboratory findings of lymphopenia are associated with a worse prognosis (severe symptoms, death, ARDS, and care in the ICU) in cases of COVID-19[12].

Current research shows that lymphopenia, which is defined as a low lymphocyte count (<1000 cells/μL), is generally present in patients with COVID-19 and the degree of lymphopenia correlates with disease severity in patients with COVID-19[13,14]. There is a correlation between lymphocyte count and the severity of COVID-19 cases. COVID-19 patients receiving treatment in the ICU had lower lymphocyte levels with an average difference of 376.53/μL (95% CI 682.84 – 70.22; p = 0.02)[12.15].

Lymphocyte count was also found to be lower in COVID-19 patients with severe symptoms (mean difference 353.34/μL; 95% CI 271.89 – 483.22; p<0.001)[13]. This study aimed to determine the relationship between lymphocyte count, mortality, and length of stay of confirmed COVID-19 patients in the COVID ICU of RSUP Dr. Sardjito.

## METHODS

This study used a retrospective cohort observational study design to assess the relationship between lymphocyte levels, mortality, and length of stay of COVID-19 patients in the COVID-19 ICU of DR Sardjito Hospital. The research was conducted at the Medical Records Installation of RSUP Dr. Sardjito, by collecting medical record data for patients with confirmed COVID-19 who examined their lymphocyte count during treatment from 1 January 2021 to 31 December 2021. This research was approved by the Ethics Committee of the Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada with the reference number KE/FK/0105/EC/2023.

The target population in the study were all COVID-19 patients receiving treatment at the ICU COVID RSUP Dr. Sardjito. The reachable population is patients indicated for hospitalization with a diagnosis of severe or critical COVID-19 confirmed by the results of a nasopharyngeal or throat swab RT-PCR examination and receiving treatment in the ICU COVID RSUP Dr. Sardjito in January – December 2021. A total sampling method was used in this study so that all patients with a diagnosis of severe or critical COVID-19 who received treatment at the ICU COVID-19 RSUP Dr. Sardjito and fulfilled the inclusion and exclusion criteria were included as research subjects.

The inclusion criteria in this study were data on lymphocyte count examination in the patient's medical record at the start of treatment and the patient was over 18 years old. Exclusion criteria in this study were patients with HIV infection, Hepatitis B, malaria, and tuberculosis and a history of comorbid malignancy such as leukemia and lymphoma.

Comparative analysis of this data was carried out between the outcome groups using the t-test. Data on a categorical scale are shown as percentages, and differences between groups of outcomes were tested by the chi-square test. Variables that are not normally distributed are expressed as the median and range (minimum-maximum), and compared using the Mann-Whitney test.

Survival analysis was also carried out to determine the relationship between lymphocyte count and mortality and length of stay using the Kaplan Meier method. Based on ROC and Youden's Index analysis, the cut-off point for lymphocyte numbers as a mortality factor was $1.06x10^3$ cells/μL, with a sensitivity of 61.3% and specificity of 64.8%, and an area under the curve of 0.606 (95% CI 0.528 – 0.694). This shows that the lymphocyte count value has acceptable discrimination in determining patient mortality outcomes.

Univariate survival analysis was also carried out using Cox Regression to evaluate the relationship of the independent variable lymphocyte count and other variables to mortality outcomes and length of stay. Meanwhile, to control for confounding factors, multivariate analysis using Cox Regression was also performed on variables that had a P value <0.25 on univariate analysis. P value < 0.05 was considered statistically significant.

## RESULTS

During the study period, 217 subjects with severe or critical degrees of COVID-19 were treated in the ICU of RSUP Dr. Sardjito and met the inclusion criteria. The median age of the patients in this study was 62 years, and 59% of the subjects were male. The median BMI of the study subjects was 24.2 kg/m2. The most common co-morbidity suffered by research subjects was hypertension (43.5%), followed by diabetes mellitus (39.2%), obesity (35.5%), and cardiovascular disease (28.55%). Most (65.4%) of the research subjects had death outcomes. Most (90.32%) of patients who were admitted to the ICU came from the resuscitation room, while 9.67% of the study subjects came from the treatment ward which had worsened so that treatment was escalated to the ICU. The median length of stay in the ICU for all subjects in this study was 154 hours or the equivalent of 6 days 10 hours (Table 1).

*Table 1. Demographic characteristics of the subjects*

| ***Parameter*** | ***Value*** |
|---|---|
| Age (years), Median (minimal-maximal) | 62 (20 – 89) |
| BMI, Median (minimal-maximal) | 24.2 (12.62 – 43.25) |
| **Sex** | |
| Male, n (%) | 130 (59.9%) |
| Female, n (%) | 87 (40.1%) |
| **Comorbidities** | |
| Diabetes Mellitus, n (%) | 85 (39.2%) |
| Hypertension, n (%) | 94 (43.5%) |
| Obesity, n (%) | 77 (35.5%) |
| Asthma, n (%) | 3 (1.4%) |
| COPD, n (%) | 8 (3.7%) |
| CKD, n (%) | 35 (16.7%) |
| Cardiovascular disease, n (%) | 64 (28.55) |
| **Outcome** | |
| Death, n (%) | 142 (65.4%) |
| a. Patients from ward, n (%) | 11 (7.7%) |
| b. Patients from resuscitation room, n (%) | 131 (92.3%) |
| Survive, n (%) | 75 (34.6%) |
| a. Patients from ward, n (%) | 10 (13.3%) |
| b. Patients from resuscitation room, n (%) | 65 (86.7%) |
| **ICU hospitalization duration (hours),** Median (minimal-maximal) | 154 (7.37 – 1383.5) |

*COPD= Chronic Obstructive Pulmonary Disease; CKD = chronic kidney disease; BMI = Body Mass Index

Table 2 provides demographic data for subjects based on outcomes. It is known that the median leukocyte count in dead subjects was significantly higher than living subjects (p = 0.021), with the median being 14.825 (1.680 – 44.030) cells 103/µL and 11.590 (2.210 – 31.370) cells 103/µl, respectively. The number and percentage of lymphocytes in living subjects were found to be significantly higher than the number and percentage of lymphocytes in deceased subjects, with the lymphocyte count in living subjects being 1.13 (0.60 – 4.70) 103 cells/µL compared to 0.79

(0.1 – 4.49) ) 103 cells/µL in dead subjects (p = 0.010), while the percentage of lymphocytes was 9.6 (0.7 - 34.60) ) in survived subjects and 6.30 (0.8 - 30.9) in dead subjects (p = 0.001).

There were no significant differences in median age, BMI, gender, comorbid hypertension, obesity, asthma, COPD, CVD, and CKD between subjects with survival and death outcomes. Meanwhile, there was a significant difference in DM comorbid, with higher DM comorbidity in the deceased patient's group (p=0,026). The length of stay variable had a significant difference (p=0.000) between living and dead subjects, with a median length of stay of 253.04 (39.03 – 1383.43) hours for living subjects and 112.99 (7.36 – 782.5) hours of stay for dead subjects.

*Table 2. Subjects Demographics Characteristics Based on Outcome*

| ***Parameter*** | ***Outcome*** | | ***P value*** |
|---|---|---|---|
| | ***Death*** | ***Survive*** | |
| Leukocyte (cells $10^3$/µL) | 14.825 (1.680-44.030) | 11.590 (2.210–31.370) | **0.021**[a] |
| Lymphocyte Count (cells $10^3$/µL) | 0.79 (0.1–4.49) | 1.13 (0.60–4.70) | **0.010**[a] |
| Lymphocyte % | 6.30 (0.8–30.9) | 9,6 (0.7-34.60) | **0.001**[a] |
| Age (years), median (min – max) | 63 (20–89) | 61 (25 – 80) | 0.059[a] |
| BMI, median (min – max) | 24.22 (14.84–39.26) | 24.22 (12.62–43.25) | 0.833[a] |
| Sex, n(%) | | | 0.574[b] |
| Male | 87 (66.9%) | 43 (33.1%) | |
| Female | 55 (63.2%) | 32 (36.8%) | |
| Comorbidities, n(%) | | | |
| Diabetes Mellitus | 48 (56.5%) | 37 (43.5%) | **0.026**[b] |
| Hypertension | 57 (60.6%) | 37 (39.4%) | 0.209[b] |
| Obesity | 52 (67.5%) | 25 (32.5%) | 0.630[b] |
| Asthma | 2 (66.7%) | 1 (33.3%) | 0.964[b] |
| PPOK | 7 (87.5%) | 1 (12.5%) | 0.181[b] |
| CKD | 20 (57.1%) | 15 (42.9%) | 0.260[b] |
| Cardiovascular disease | 42 (65.6%) | 22 (34.4%) | 0.970[b] |
| Hospitalization duration (hours), median (min – max) | 112.99 (7.37–782.5) | 253.04 (39.03 – 1383.43) | **0.000**[a] |

*BMI*: body mass index,* COPD= *Chronic Obstructive Pulmonary Disease*, CKD*: chronic kidney disease,*

The cut-off points for lymphocyte count as a mortality factor was determined based on the analysis of the ROC (Receiver Operating Characteristic) curve and Youden's Index to determine the optimum point. Based on ROC and Youden's Index analysis, the cut-off point for lymphocyte count as a mortality factor was 1.06,103 cells/µL, with a sensitivity of 61.3% and a specificity of 64.8%, and an area under the curve of 0.606 (95% CI 0.528 – 0.694). This shows that the lymphocyte count has acceptable discrimination in determining patient mortality outcomes (Figure 1). With a lymphocyte number cut-off point of 1.06,103 cells/µL, a basic characteristic is produced based on a low lymphocyte number (<1.06,103 cells/µL) and a high lymphocyte

number >1.06,10³ cells/µL). From these results, 121 (55.8%) study subjects had low lymphocytes <1.06,10³ cells/ µL) and 96 (44.2%) study subjects had high lymphocytes > 1.06,10³ cells/ µL.

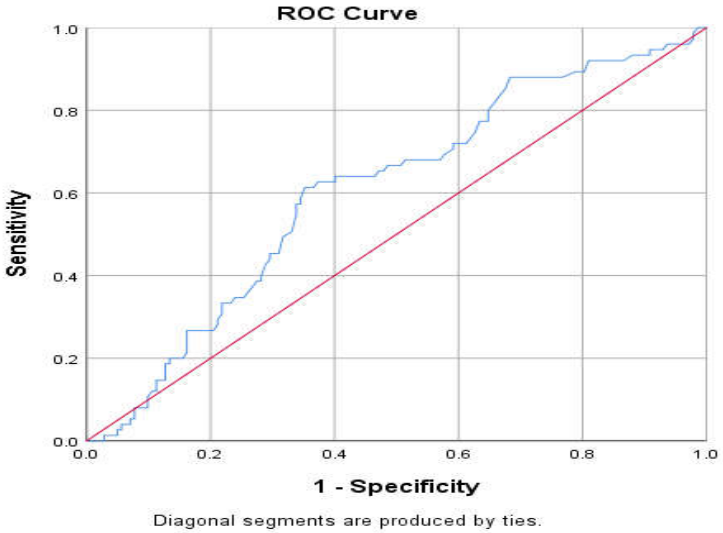


*Figure 1. ROC (Receiver Operating Characteristic) Curve Based on the Correlation Between Lymphocyte Count and Mortality Events*

There were statistically significant differences in the median/proportion for several variables, namely age (p=0.034), BMI (p=0.021), and mortality outcome (0.000). Subjects had a median older age in the group with low lymphocyte counts (median 63 years), compared to high lymphocyte counts (median 61 years). Meanwhile, the patient's BMI tended to be higher in the group of subjects with high lymphocyte count (24.57 kg/m2) compared to low lymphocyte count (23.44 kg/m2). Based on the outcome, of the 142 patients who died, the majority (64.8%) came from a group of subjects with low lymphocyte counts. In contrast, most of the surviving patients (61.3%) were from the group with high lymphocyte counts. This shows that patients with lower lymphocyte counts were 2.919 times more at risk of experiencing mortality (95% CI 1.637 – 2.204; p=0.000). These results are still quite in line with the hypothesis that decreased lymphocyte count are associated with mortality in patients with severe and critical degrees of COVID-19 who are hospitalized at RSUP Dr. Sardjito (Table 3).

Analysis of length of stay in the ICU based on lymphocyte values was analyzed using Kaplan-Meier and cox regression univariately. From this analysis, it was found that the lymphocyte count <1.06,10³ cells/ µL had a shorter duration of stay in the ICU (median 128.77 hours) but was not statistically significant (OR 0.802, 95% CI 1.032 – 2.646; p=0.110).

Lymphocyte count, age, and cardiovascular disease have a significant correlation with the occurrence of mortality. Patients with high lymphocyte counts had a reduced risk of dying (HR

0.570; 95% CI 0.403 – 0.807, p=0.002). This suggests that decreased lymphocyte levels are associated with an increased likelihood of mortality. In addition, the older the patient, the higher the risk of experiencing mortality (HR 1.015; 95% CI 1.002 – 1.028, p=0.019). Another variable that has a significant effect is comorbid cardiovascular disease. Having a history of cardiovascular disease increases the risk of death by up to 1.471 times (HR 1.471; 95% CI 1.016 – 2.128, p=0.041).

*Table 3. Subjects Demographics Data Based on Lymphocyte Count Cut-off Point as Mortality Predictor*

| **Parameter** | **Lymphocyte Count (cells $10^3$/µL)** | | **P *value*** |
|---|---|---|---|
| | **< 1,06** | **≥ 1,06** | |
| Age (years), median (min – max) | 63 (25 – 87) | 61 (20 – 89) | 0.034[a] |
| BMI, median (min – max) | 23.44 (14.8 – 37.9) | 24.57 (12.62 – 43.24) | 0.021[a] |
| Sex | | | 0.124[b] |
| Male, n(%) | 78 (60.0%) | 52 (40.0%) | |
| Female, n(%) | 43 (49.4%) | 44 (50.6%) | |
| Comorbidities | | | |
| Diabetes Mellitus, n (%) | 51 (60.0%) | 34 (40.0%) | 0.313[b] |
| Hypertension, n (%) | 52 (55.3%) | 42 (44.7%) | 0.856[b] |
| Obesity, n (%) | 37 (48.1%) | 40 (51.9%) | 0.090[b] |
| Asthma, n (%) | 2 (66.7%) | 1 (33.3%) | 0.702[b] |
| COPD, n (%) | 7 (87.5%) | 1 (12.5%) | 0.066[b] |
| CKD, n (%) | 21 (60.0%) | 14 (40.0%) | 0.581[b] |
| Cardiovascular disease, n (%) | 37 (57.8%) | 27 (42.2%) | 0.694[b] |
| Outcome, (%) | | | 0.000[b] |
| Death, (%) | 92 (64.8%) | 50 (35.2%) | |
| Survive, (%) | 29 (38.7%) | 46 (61.3%) | |
| $X^2$ | OR (95%CI) = 2.919 (1.637 – 2.204)[b] | | |
| Hospitalization duration (hours), median (min-max) | 128.77 (12.84 – 983.99) | 164.69 (7.37 – 1383.43) | 0.110[c] |
| | OR (95% CI) = 0.802 (1.032 – 2.646)[c] | | |

*BMI*: body mass index,* COPD= Chronic Obstructive Pulmonary Disease*,* CKD*: chronic kidney disease,* CI: *Confidence Interval,* OR: *Odds Ratio*

Several variables had p<0.25 on univariate analysis, namely lymphocyte count, age, DM, hypertension, and cardiovascular disease. These variables were then analyzed by multivariate. The results of the multivariate test showed that the lymphocyte count was the most significant independent variable in determining mortality (HR 0.584; 95% CI 0.411 – 0.830; p=0.003). Besides lymphocyte count, age (HR 1.015; 95% CI 1.002 – 1.029; p=0.023), presence/absence of comorbid hypertension (HR: 1.573; 95% CI 1.124 – 2.313; p=0.010), presence/absence of comorbid cardiovascular disease (HR: 1.542; 95% CI 1.042 – 2, 283; p=0.030) are factors that

independently and significantly influence the incidence of mortality in patients with severe to critical degrees of COVID-19 at Dr. Sardjito.

*Table 4. Univariate and Multivariate Analysis of Lymphocyte Count and Other Mortality Predictors*

| Parameter | Univariate | | | Multivariate | | |
|---|---|---|---|---|---|---|
| | HR | 95%CI | P-Value | HR | 95% CI | P-Value |
| Lymphocyte Count | 0.570 | 0.403 – 0.807 | 0.002* | 0.584 | 0.411 – 0.830 | 0.003 |
| Sex | 0.942 | 0,672 – 1,322 | 0,576 | | | |
| Age | 1.015 | 1.002 – 1.028 | 0.019* | 1.015 | 1.002 – 1.029 | 0.023 |
| BMI | 0.995 | 0.963 – 1.029 | 0.774 | | | |
| **Comorbidities (Yes/No)** | | | | | | |
| DM | 1.242 | 0.877 – 1.759 | 0.222* | 1.224 | 0.862 – 1.737 | 0.259 |
| Hypertension | 1.320 | 0.941 – 1.852 | 0.123* | 1.573 | 1.124 – 2.313 | 0.010 |
| Obesity | 1.005 | 0.713 – 1.418 | 0.975 | | | |
| Asthma | 1.708 | 0.422 – 6.919 | 0.453 | | | |
| COPD | 1.138 | 0.531 – 2.439 | 0.740 | | | |
| CKD | 1.144 | 0.713 – 1.837 | 0.577 | | | |
| CVD | 1.471 | 1.016 – 2.128 | 0.041* | 1.542 | 1.042 – 2.283 | 0.030 |

BMI*: body mass index,* COPD= Chronic Obstructive Pulmonary Disease, CKD*:* chronic kidney disease, CVD: Cardiovascular disease

Kaplan-Meier analysis showed that the group of subjects with a lymphocyte count <1.06,10$^3$ cells/µL had a shorter survival time, namely 178.18 hours, compared to the group of patients with a lymphocyte count >1.06,10$^3$ cells/µL, which was 368.24 hours. This shows that the increase in lymphocyte count significantly increases the overall survival of patients with severe and critical degrees of COVID-19 (p=0.001) (Figure 2).

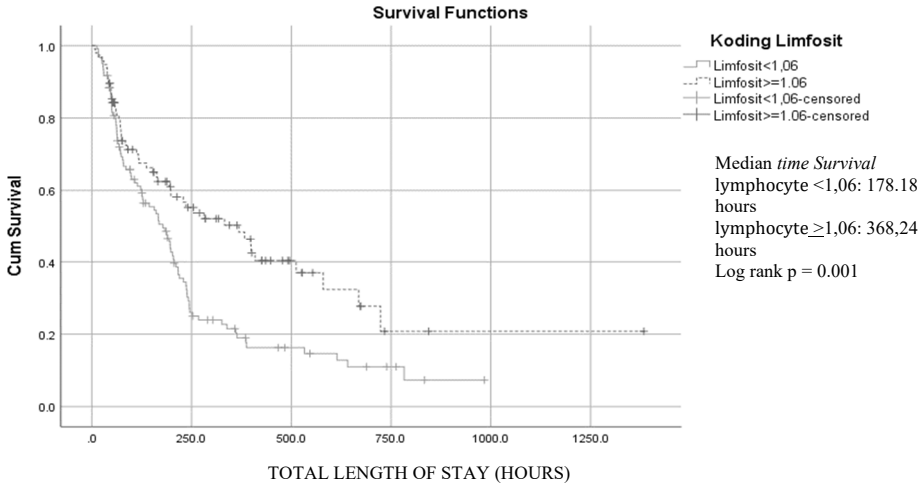


*Figure 2. Kaplan Meier Survival Analysis based on Lymphocyte Count*

## DISCUSSION

During the study period, 217 subjects with severe or critical degrees of COVID-19 were treated in the ICU of RSUP dr. Sardjito and met the inclusion criteria. The median age of the patients in this study was 62 years, and 59% of the subjects were male. The median BMI of the study subjects was 24.2 kg/m2. The most common co-morbidity suffered by research subjects was hypertension (43.5%), followed by diabetes mellitus (39.2%), obesity (35.5%), and cardiovascular disease (28.55%). Most (65.4%) of the research subjects had death outcomes. The number and percentage of lymphocytes in living subjects was found to be significantly higher than the number and percentage of lymphocytes in deceased subjects, with the lymphocyte count in living subjects being 1.13 (0.60 – 4.70) 103 cells/µL compared to 0.79 (0.1 – 4.49) ) 103 cells/µL in dead subjects (p = 0.010), while the percentage of lymphocytes was 9.6 (0.7 - 34.60) ) in survived subjects and 6.30 (0.8 - 30.9) in dead subjects (p = 0.001). There were no significant differences in median age, BMI, gender, comorbid hypertension, obesity, asthma, COPD, and CKD between subjects with survival and death outcomes.

### Patient demography and lymphocyte levels relationship

The median age of lymphocytes below and above 1.06,$10^3$ cells/µL was more or less the same, only slightly higher in the <1.06,$10^3$ cells/µL group, namely 63 and 61 years. This is in line with research by Liu et al, which stated that the median age of patients with lymphopenia was lower than those without lymphopenia[15]. A higher age was found in a study by Illg et al, 2021, which stated that the age found in the mean form was 67.1 years[17]. Another study by Selanno et al, showed a trend of younger age, namely 40.8 ± 14.5 years, but this study used the meanwhile this study used the median. The younger age in this study is suspected because productive age has higher mobility and activity, causing a higher spread of COVID-19 and more likely to contract COVID-19[19]. BMI was higher in the group >1.06,$10^3$ cells/µL with a median of 24.57kg/m2 compared to the group <1.06,$10^3$ cells/µL with a median of 23.44kg/m2. The study by Niu et al supports the results of this study, higher rates of obesity in the group of patients with lymphopenia <1.1,$10^3$ cells/uL[18].

### Length of stay predictor

In this study, the median duration of stay in the ICU in patients with lymphocyte count <1.06,$10^3$ cells/µL was 128.77 hours and >1.06,$10^3$ cells/µL was 164.69 hours, these results were not statistically significant (OR 0.802, 95% CI 1.032 – 2.646; p=0.110). Analysis of patient survival

using Kaplan Meier and univariate Cox regression, it can be concluded that the lymphocyte count <1.06,$10^3$ cells/µL reduced the duration of stay in the ICU with a shorter survival time (178.18 hours vs 368.24 hours, p=0.001). These results were supported by a study by Alagbe et al., which stated that lymphocyte count had a negative correlation with mortality and COVID-19 severity and was recommended as a parameter for predicting patient outcomes for COVID-19[20]. The study by Wang et al. also supports this study, that a decreased peripheral lymphocyte count is associated with increased mortality in COVID-19 patients and has the potential to predict the prognosis of death in hospitalized COVID-19 patients[21]. Lymphopenia correlates with hyperinflammatory response, which is characterized by serum levels of C-reactive protein (CRP). ), high IL-6, D-dimer, and LDH, which are known to be associated with worse severity and outcome of COVID-19. Physiologically, the mechanism thought to link lymphopenia to poor clinical outcomes in COVID-19 specifically involves T lymphocytes. A higher total T lymphocyte count, including CD4+ and CD8+, has been shown to be a predictor of milder severity and better clinical outcome in patients with COVID-19. Approximately 70–80% of lymphocytes circulating in the peripheral blood are T lymphocytes and the main cause of lymphopenia in severe cases of COVID-19 is related to T lymphocyte apoptosis. Excessive production of proinflammatory cytokines, such as TNF-α and IL-6, can cause strong lymphocyte apoptosis. Apoptotic T lymphocytes can release Fas Ligand, which can induce excessive epithelial cell apoptosis and inflammation, resulting in pulmonary fibrosis. Lymphopenia was consistently found to be independently associated with adverse clinical outcomes, namely ICU stay, use of mechanical ventilation, dialysis, and death.[18] This suggests that a low lymphocyte count reflects worse mortality in COVID-19 patients.

## Mortality predictors

Univariate and multivariate analyses using Cox regression were carried out in this study to assess the effect of the relationship between independent variables/confounders on mortality. The results showed that in the univariate test, there were 3 statistically significant variables related to mortality in the subjects, namely lymphocyte count (p=0.002), age (p=0.015), and cardiovascular disease (p=0.041). Patients with higher lymphocyte counts had a reduced risk of dying (HR 0.570; 95% CI 0.403 – 0.807, p=0.002). These results are in line with Niu et al, that higher lymphocytes, both CD4+ and CD8+, are associated with a better prognosis[18]. From these results, it was found that the lymphocyte count was the variable that was independently most significant in determining the incidence of mortality in the study subjects (HR 0.584; 95% CI 0.411 – 0.830; p=0.003).

The lymphocyte variable is an independent variable and is significantly associated with increased mortality in COVID-19. This is in line with a study by Simon et al, which stated that lymphopenia was the most significant biochemical parameter in COVID-19 mortality (OR: 2.23, 95% CI: (1.23–4.05), p = 0.009)[22]. In addition to lymphocytes, age (HR 1.015; 95% CI 1.002 – 1.029; p=0.023) is also a patient demographic variable that is related independently and significantly to the increase in mortality in COVID-19 patients. The risk factor for age as an independent variable for COVID-19 mortality is supported by a study from Rachmawati et al which stated that the elderly category has a 3-fold risk of mortality compared to non-elderly (OR 3.1 [2.6-3.7])[23]. According to studies from Elo et al and Iaccarino et al, the mortality rate increases with age. Age is the most important determinant of death in COVID-19 patients[24,25].

Two comorbidities were predictors of death outcomes in multivariate analysis, namely hypertension and history of cardiovascular disease. Hypertension increased the risk of death by 1.573 (HR: 1.573 95% CI 1.124 – 2.313; p=0.010). Having a history of cardiovascular disease increases the risk of death by 1.542 times (HR: 1.542; 95% CI 1.042-2.283; p=0.03). Hypertension is an independent risk factor for the severity and mortality of COVID-19. Hypertension is thought to be associated with the risk of SARS-COV-2 infection due to ACE-2 receptor activity. Angiotensin-converting enzyme 2 (ACE2) receptors are receptors that play a role in modulating blood pressure and building blood pressure homeostasis, as well as being receptors where SARS-COV-2 enters cells[26].

The results of a study on cardiovascular disease in COVID-19 mortality were discussed by Vasbinder et al., who stated that cardiovascular disease was a risk factor and was associated with a 1.15-fold increase in mortality (95% CI 0.98-1.34) although there was no independent association between cardiovascular disease and emergency cardiovascular events in COVID-19. The results of this study were also in line with the study by Cordero et al., which stated that cardiovascular disease was associated with an increased mortality of up to 4 times (OR 4 .33; 95% CI 3.16-5.94)[27].

In multivariate analysis, diabetes mellitus (DM) did not have a significant effect on mortality from COVID-19. However, DM is associated with the incidence of heart disease. From a meta-analysis study that analyzed 57 studies with a total of 4,549,481 type 2 DM patients, it was found that 32.2% of type 2 DM patients had cardiovascular disease. As many as 21.2% of type 2 DM patients had coronary artery disease (CAD), 14.9% had congestive heart failure (CHF), 14.6% had angina pectoris, and 10% had myocardial infarction. In DM patients, a vascular redox state occurs which results in the activation of proinflammatory toll-like receptor (TL) and nuclear factor (NF-κB) signaling which causes chronic inflammatory conditions, chronic inflammatory conditions

cause prothrombotic conditions, so DM patients are prone to occlusion which causes infarction of the coronary arteries, lower extremities, and brain[28].

The results of this study indicate that COPD and CKD increase the risk of death in COVID-19 patients, although not statistically significant (p>0.05). The results of this study are similar to the findings of Meza et al. In that study, it was found that COPD and CKD significantly increased the risk of death in COVID-19 patients. The relationship between the two co-morbidities and death from COVID-19 in this study was statistically significant, with ORs of 2.07 (95% CI 1.93 – 2.22) and 2.09 (95% CI 2.00 – 2.19) respectively. Possible mechanisms underlying the increased risk of death from COVID-19 in COPD patients include increased bronchial epithelial cell expression of ACE-2 expression, which is known to be required for infection. Other potential factors include poorer baseline lung function and lower oxygen levels in COPD patients[29].

In this study, CKD increased the risk of death from COVID-19 to 1.144 but was not statistically significant (HR 1.144; 95% CI 0.713 – 1.837). The findings of this study approximate those of a meta-analysis by Jdiaa, et al. This meta-analysis estimates that CKD can increase the risk of death from COVID-19 up to 1.48 times (HR 1.48; 5% CI 1.33 – 1.65). Some of the main causes of morbidity and mortality in patients with CKD are infection, sepsis, and bacteremia, including infection with SARS-COV-2[30].

## CONCLUSION

Low lymphocytes <1.06,$10^3$ cells/µL in COVID-19 patients are independently and significantly associated with increased risk of mortality and insignificantly associated with shorter length of stay.

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