CORRELATION OF LYMPHOCYTE-MONOCYTE RATIO AND MORTALITY OF COVID-19 INTENSIVE CARE UNIT PATIENTS: PRELIMINARY STUDY

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ABSTRACT

Background: *The world faces a pandemic caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-Cov-2). Because of the limitations as a developing country, Indonesia needs to do its activities efficiently in time, money, and human resource. This research aims to accurately determine a concrete mortality predictor to predict the patients' mortality. One of the mortality predictors is the lymphocyte-monocyte ratio (LMR).*

Method: *This research is observational analytic research using a cross-sectional study method. Data obtained from the Medical Record & Casemix Room of RSUD Raden Mattaher.*

Results: *Out of 115 samples, most patients were male (65 patients). The patients' age group was mainly younger than 65 (79%). The most common comorbidity was diabetes mellitus (43 patients). The correlation between LMR and mortality rate to be weak with the following results: Pearson coefficient(p=0.045), gamma coefficient (P=0.325), Somers' D test (P=0.167), odds ratio (1.833), AUC (58%), specificity (58%), sensitivity (56%), and intersection point (1,79).*

Conclusions: *There is a weak correlation between LMR and the mortality rate of COVID-19 patients in RSUD Raden Mattaher.*

Keywords*: Characteristics of COVID-19 patients, comorbidity of COVID-19 patients, LMR (Lymphocyte-monocyte ratio), a mortality rate of COVID-19 patients*.

INTRODUCTION

Currently, the world is experiencing a pandemic of the pneumonia series caused by a virus with severe acute respiratory syndrome coronavirus 2 (SARS-Cov-2). SARS-Cov-2 is a typical virus belonging to the RNA virus with unique characteristics resembling a crown and surrounded with spines made of glycoprotein. The coronavirus itself has several types, namely α-coronavirus (alphaCoV), β-coronavirus (betaCoV) which usually appears in bats or mice, δ-coronavirus (deltaCoV), γ-coronavirus (gammaCoV) which usually occurs in birds.[1]

At the end of 2019 in Wuhan, there were cases of pneumonia that eventually spread to the world and entered parts of Indonesia. As we know, with the coronavirus disease 2019 (COVID-19) entry into the territory of the Unitary State

of the Republic of Indonesia, Indonesia itself is still included in one of the developing countries with a population of 268.074 million. Alternatively, other sources will experience a significant decrease.[2] So, with current conditions, we must carry out all activities efficiently in terms of time, finance, or energy due to limitations in this regard.[1,3] In helping the process of preventing or treating COVID-19 patients themselves, it is necessary to have a diagnosis process with several concrete methods to predict mortality accurately and help reduce mortality rates in COVID-19 patients in the Intensive Care Unit (ICU), especially Raden Mattaher Hospital itself. One of these predictors can use routine blood data consisting of specific variables to determine the patient's condition. One of these variables is Lymphocyte-Monocyte Ratio (LMR).[4]

Lymphocyte-Monocyte Ratio calculates the ratio between lymphocyte and monocyte count obtained through routine blood samples. COVID-19 patients generally have increased leukocytosis, neutrophilia, lymphocytopenia, and monocytosis. Generally, LMR itself is used as an indicator or biomarker in patients with cardiac disorders due to the increased activity of monocytes themselves which can transform into megakaryocytes which will affect the production of proinflammatory cytokines secretion, matrix metalloproteinases, and reactive oxidative species where this is the primary key and which play a role in the rupture of atherosclerotic plaques.[4] Lymphocytes represent potentially critical immune cells in cardiovascular disease. Due to increased lymphocyte apoptosis, lymphocytopenia is a common sign of a chronic inflammatory state. LMR itself is expected to be the latest predictor of mortality in providing additional information to determine systemic inflammation status and is easily obtained through routine blood tests. It is suspected that there is a dynamic decrease in LMR while in the hospital ICU so, it can be used as a measuring tool for the severity and prognosis of the disease itself.[5]

In research conducted by Prabhu S., Nishant Patil in Karnataka, India. As stated in a study conducted on 100 patients, the cut-off point was 2.1 for LMR showing a sensitivity of 82.4% and specificity of 84.8%, and the optimal threshold at 317.52.[5]

The LMR biomarker obtained through routine blood tests is hoped to be used as an efficient, inexpensive, and concrete biomarker to predict mortality and carry out appropriate interventions to reduce the incidence of mortality COVID-19.

METHODS

The following research uses an analytic observational method with a cross-sectional study and a correlative hypothesis test. This research was conducted at the Medical Record Installation at Raden Mattaher Hospital

Jambi. The study was conducted from July 2021–October 2021.[6]

The population in this study were all patients with a positive diagnosis of COVID-19. The sample in this study were patients with a positive diagnosis of COVID-19 in the ICU of RSUD Raden Mattaher Jambi from April 2020 - March 2021. The research sample will be more specifically included in the inclusion criteria where the criteria are Patients with a positive diagnosis of COVID-19 with age more than the same with 18 years and treated in the ICU RSUD Raden Mattaher Jambi.

Sampling was carried out by taking data from the medical records of COVID-19 patients treated in the ICU at Raden Mattaher Hospital using the Purposive Sampling method. This method determines the sample based on inclusion & exclusion criteria.[7,8] The minimum sample size required will use the Slovin formula because the characteristics of the population are not known with certainty. By using that formula, the minimum sample size for this study is 80 patients.[9]

This study uses secondary data where the data collected is medical record data of patients diagnosed as positive for COVID-19 obtained from the ICU medical records of Raden Mattaher Jambi Hospital. The tools used are research data forms & stationery. The data taken are the characteristics of the demographic data of the patient's name, age, gender, occupation, and the results of routine blood tests & patient outcomes. Data were analyzed using the bivariate analysis method correlatively with the Pearson/Spearman test and processed using Statistical Product and Service Solutions (SPSS) software.[7,8]

RESULTS

The sampling results conducted in the case mix and medical record room at RSUD Raden Mattaher Jambi found that the number of samples was 150 people, and as many as 26 sample data did not enter the inclusion criteria so that they were included in the exclusion data. A sample of 124 people was obtained with inclusion criteria, namely positive COVID-19 patients and those aged over 65 years. Data processing was carried out using the Microsoft Excel program and the SPSS Version 16 program from these samples. After processing the program's data, the optimal sample was obtained to produce the best results, namely 115 samples from 124 samples obtained. The sample sorting process is carried out using the outliers technique in the SPSS program.

In principle, the outliers technique is to sort out data with extreme data values, where extreme values in the data can cause changes in the normality distribution of the data and the relationship between the variables. So with the application of this technique, researchers can find the correct data and maximum results in data processing.[10]

From the data normality test using the Kolmogorov-Smirnov test method, a significance value of 0.104 was obtained where the value was above the value >0.05 so that the data were normally distributed. In this data, only LMR data can be tested for normality because mortality data is data with a categorical scale and the probability distribution of the data is discrete data that is not continuous, so it cannot be tested for normality. In the Pearson correlation test data, a significance value of 0.045 was obtained where the value was below the value (p <0.05), then the data between the LMR variable and mortality could be said to be a related variable. In the results of the Gamma Sommers Coefficient test data, the Sommers data results with a value of 0.167, where this value states that the LMR relationship that has been grouped based on high and low is weak related to mortality. Furthermore, the value of Gamma Coefficient, a value of 0.325, is obtained above the value (P> 0.05), then these variables can be said to be related. The Odds Ratio results are 1.833, which means that patients with low LMR have 1.833 times mortality compared to patients with high LMR.[11]

Table 1. Pearson Correlation Test Results, Sommers Gamma Coefficient, and Odds Ratio

Classification	*Pearson (Ratio)*	*Sommers (Ordinal)*	*Coefficient Gamma (Ordinal)*	*Odds Ratio*
LMR	*0.045*	*0.167*	*0.325*	*1.833*

The cut-off point determines the LMR limit value at Raden Mattaher Jambi Hospital. The determination uses the convergence technique between specificity & sensitivity using the Microsoft Excel program. In the Cut-Off graph of sensitivity and specificity, the Cut-Off value is 1.79 with the convergence graph technique and the sensitivity value is 56%, and specificity is 58%.[11]

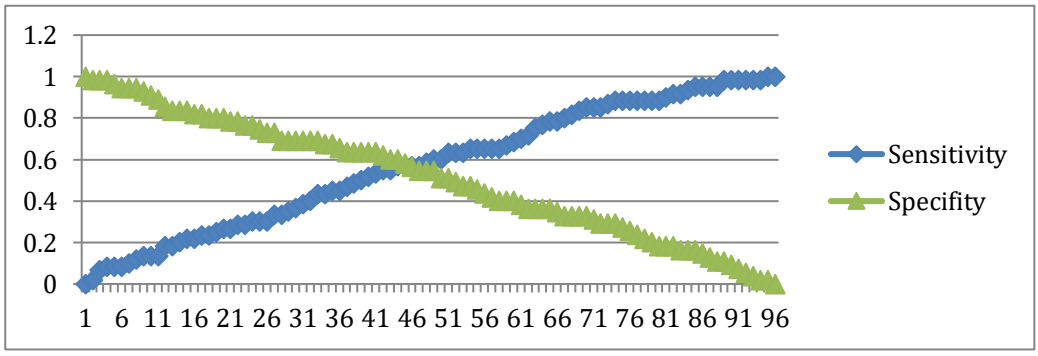

Figure 1. Cut-Off Meeting Point Image

In addition, researchers wanted to determine the accuracy of LMR as a predictor of mortality by looking at the AUC (Area Under the Curve). The determination uses the ROC graph technique; in the graph below, the blue LMR variable line looks close to the median value of sensitivity and specificity so that it can be said that the results of the relationship between the LMR variable and mortality seem less good or appear weak.[11]

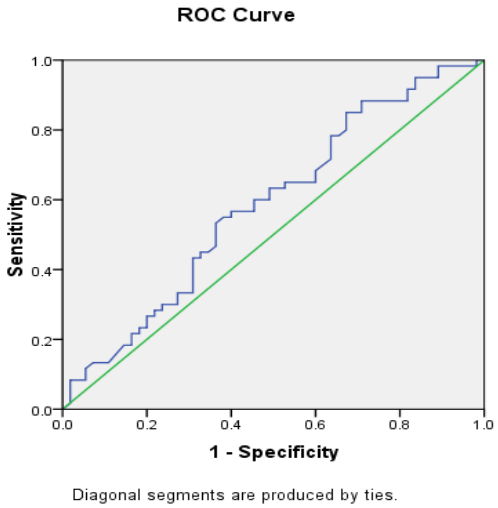

Figure 2. Graphic ROC

In the AUC value data, the value from the area under the blue line is 0.58, or if it is used as a percent, it is 58%, which means the ability of the LMR ratio in this study, as a marker that can predict the occurrence of mortality, is included in the category of mortality predictors with weak accuracy, which is true, there will be mortality (sensitivity) of 56% and will correctly predict no mortality (specificity) of 58%.[11]

Table 2. Analysis Results

Classification	*AUC*	*Cut Off Value*	*Sensitivity*	*Specificity*	*Confident Interval 95%*	
					Lower	*Upper*
Ratio LMR	*0.58*	*≤ 1.79*	*0.56*	*0.58*	*0.481*	*0.69*

Based on further research data, the number of characteristics of research subjects related to the LMR value was obtained, namely:

Table 3. Table of Characteristics of Research Subjects with LMR Values

Characteristics Patients	LMR Value	
	<1.79 (Lower)	>1.79 (Upper)
Gender		
Man	33*	32*
Women	22*	28*
Age		
≥ 65	14*	10*
18≤….< 65	41*	50*
Comorbidity		
Diabetes Mellitus	22*	21*
Hypertension	18*	11*
Pneumonia	4*	1*
Asthma	Nothing	1*
Aritmia	3*	1*
Chronic Kidney Diseases	7*	6*
Acute Kidney Injury	2*	3*
Unstable Angina Pectoris	Nothing	2*
Coronary Artery Diseases	2*	1*
Bronchopneumonia	3*	4*
Anemia	3*	Nothing
Outcome		
Died	33*	27*
Lived	22*	33*

* = Person

Patients with COVID-19 associated with the LMR cut-off point were dominated by men (65 people) compared to women (50 people); the most age was less than 65 years old (91 people), the most common comorbidity was diabetes mellitus (43 people). Moreover, it has a high mortality rate (60 people died).

DISCUSSION

In a study conducted by Jahja T Widjaja et al. (2021), a sample of 48 patients was taken by looking at the clinical characteristics, comorbidities, therapy, and patient outcomes. It was found that women dominate 52.4%, age range 50-60 years, patients die 25%, the most significant comorbid hypertension. There are similarities, namely the group under 65 years of age that dominates.[12]

In a study conducted by Prabhu et al. (2021), The process was carried out by collecting data from 100 laboratory-confirmed patients and determining the effect of gender, age, CRP, WBC count, NLR, LMR, PLR, and comorbidities on the length of stay of patients with COVID-19 pneumonia. It was found that male-dominated 67 people, age was not grouped, the most significant comorbid hypertension was 28 people. There are similarities in the researcher's research with Prabhu's research, namely that men equally dominate. In addition, the results of laboratory calculations showed that the Monocyte to Lymphocyte ratio was an acceptable efficiency by showing the

optimal threshold of 2.1 LMR with a sensitivity of 82.4% and a specificity of 84.8%. The value of the AUC LMR in this study by Prabhu was also obtained, which was 0.101, where if the percentage were only 10%, it would be difficult if the LMR was used as a biomarker because the relationship was fragile. So, there are similarities in the results of this study; namely, there is a relationship with weak accuracy in LMR with mortality in COVID-19 patients.[5]

According to research conducted by Satria et al. (2020), that gender is proven to be a risk factor for mortality in COVID-19 patients, where men die more than women. This is because there are fundamental differences in the immunological systems of men and women, differences in lifestyle, and smoking prevalence—fewer men recovered than the group who died. Higher mortality rates are associated with higher chronic comorbidities in men, e.g., cardiovascular disease, hypertension, pulmonary disease, and smoking. The age factor appears to be a crucial factor for the mortality of COVID-19 patients. The mean age of patients who died was 68 years and was significantly older than patients who recovered.

Furthermore, 80% of deaths in COVID-19 are adults, namely 65 years; then, old age can be a risk factor for COVID-19 mortality. The percentage of COVID-19 mortality increases; comorbid diabetes and heart disease suffered by COVID-19 patients can be a risk factor for death. The prevalence of diabetes patients hospitalized due to COVID-19 is 14.34%, whereas, in patients in Asian countries, it is 11.06%. This is lower than the prevalence in non-Asian countries is 23.34%. These diabetic patients have a two times greater risk of developing severe or critical illness requiring treatment in the intensive care unit. In hospitalization, patients with diabetes mellitus are three times at risk of dying from COVID-19. Diabetes mellitus is a risk factor independent of age and sex. due to increasing age, with the youngest patients being 5% to the oldest 55%.[13]

It can be said that LMR has a weak relationship with mortality in research according to research conducted by Prabhu S and his theory regarding COVID-19, which functions as a relative function of neutrophilia, lymphopenia, and monocytosis. A different mechanism of lymphopenia in COVID-19 patients has been associated with the ability of the virus to infect T-cells via the Angiotensin-Converting Enzyme 2 (ACE2) receptor and the cluster of differential (CD)147-spike protein. The result is a decrease in CD3+, CD4+, CD8+ T lymphocytes. Then regulatory T cells become increased. The emergence of proinflammatory cytokines with T-cell lymphopenia predisposes severe COVID-19 patients to cytokine storm, resulting in more lymphocyte apoptosis and multi-organ failure. Overall, decreased levels of CD4+ and CD8+ T

lymphocytes correlated with disease severity, which can lead to low LMR.[5]

CONCLUSION

There is a weak relationship between the LMR variable and mortality. Patients with COVID-19 associated with the LMR cut-off point were dominated by men (65 people) compared to women (50 people); the most age was less than 65 years old (91 people), the most common comorbidity was diabetes mellitus (43 people). Furthermore, it has a high mortality rate (60 people died). The cut-off point for LMR is 1.79. LMR accuracy in assessing mortality is included in the category of diagnostic markers with weak accuracy with an AUC value of 58%, sensitivity 56%, and specificity of 58%.

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Author Contribution

dr. Ade Susanti was involved in planning and supervised the work, dr. Fairuz performed the measurements, processed the experimental data, performed the analysis, drafted the manuscript, and designed the figures. Muhammad Fadhil Naufal performed the data calculations and statistical analysis. Muhammad Fadhil Naufal, dr. Ade Susanti and dr. Fairuz aided in interpreting the results and worked on the manuscript. All authors discussed the results and commented on the manuscript.

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