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Association between Lymphocyte-to-Monocyte Ratio and Survival in COVID-19 Infected Patients

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Early identification of patients who may develop into clinical deterioration is necessary to prevent complications and death from COVID-19. This research aims to determine the association between lymphocyte-to-monocyte ratio (LMR) and survival in Coronavirus disease-2019 (COVID-19) patients. This study used a retrospective cohort design. We collected survival data retrospectively by tracing medical records to gather data on demographic, clinical, and laboratory characteristics. Mann-Whitney U test was used to determine the difference in LMR values in the survivor and non-survivor groups. A total of 502 subjects were involved in this study. The LMR value was significantly lower in the non-survivors group compared to the survivors group (p=0.001). We found an adjusted odds ratio (OR) of LMR of 3.62; 95% confidence interval (CI) 1.92-14.25; p=0.046). LMR can reflect the disease severity and can be used to predict prognosis.

Keywords: COVID-19, lymphocyte, monocyte, survival.

The coronavirus disease 2019 (COVID-19) has caused a pandemic and extraordinary health impacts. Most patients show mild clinical symptoms, but some can experience severe clinical symptoms with severe acute respiratory distress syndrome.[1,2]. Death often occurs in patients with co-morbidities or the elderly[3].

Because the symptoms of COVID-19 can develop into serious complications, it is crucial to identify patients who may experience clinical deterioration at an early stage. Routine examinations such as a complete blood count (CBC) can be a quick and easy examination to predict prognosis[4,5]. Studies show that the worsening of clinical symptoms in COVID-19 is closely related to immune system dysregulation[6,7]. Inflammatory biomarkers originating from the peripheral blood, such as neutrophils, lymphocytes, and platelets, have been studied to predict prognosis in ARDS patients[8].

The severity of COVID-19 is related to the proportion of circulating immune cells[9]. Clinical symptoms in COVID-19 are influenced more by the exaggerated inflammatory response than by the direct effects of viral replication. Lymphopenia is the most common hematological change in patients with COVID-19[10]. In patients with severe clinical symptoms, a decrease in lymphocyte count may be

accompanied by an increase in monocyte count[11]. Lymphocyte-to-monocyte ratio (LMR) can be used as a clinical biomarker to monitor disease progression in COVID-19 infection.

Few studies have reported the role of the LMR as a prognostic marker in COVID-19. This study aims to determine the association between LMR and survival so that LMR can be used to predict prognosis in COVID-19 patients.

METHODS

Study design and sample

This study was conducted at Udayana University Hospital from January to April 2023 using a retrospective cohort design. Data collection is through a medical record review of all the variables studied. The sample was patients aged 18 years or older treated at Udayana University Hospital from June 2021 to June 2022. Patients who died unrelated to COVID-19 infection, had hematological diseases (such as aplastic anemia, myelodysplastic syndrome, and leukemia), and pregnancy was excluded from this study.

Data collection

SARS-CoV-2 infection was confirmed through naso-oropharyngeal swab examination and analyzed by polymerase chain reaction (PCR). The lymphocyte-to-monocyte ratio is calculated by comparing the absolute lymphocyte count and absolute monocyte count based on the results of a complete blood count examination. Survival data were collected from patient medical records and followed up retrospectively to determine demographic, clinical, and laboratory results.

Statistical analysis

We used median (interquartile range/ IQR) to present numerical variables and frequency (percentage) to present categorical variables. We used the Mann-Whitney U test to determine the difference in LMR values between non-survivors and survivors. We used the Receiver Operating Characteristic (ROC) to determine the cut-off and area under the curve (AUC) of the LMR value in predicting death in COVID-19 patients. We performed multiple logistic regression analyses to determine factors that influence survival, such as age and underlying disease. Statistically significant

Table 1. Characteristics of the subject

	Non-survivors (n=14)Median (IQR)	Survivors(n=488) Median (IQR)	p-value
Age, years	61 (44 – 74)	42 (18 – 84)	<0.001
Sex, n (%)			
Male	11 (78.6)	298 (60.4)	0.266
Female	3 (21.4)	195 (39.6)	
Underlying disease			
Without underlying disease	4 (28.6)	395 (80.1)	<0.001
With underlying disease	10 (71.4)	98 (19.9)	
Hemoglobin, gr/dl	13.1 (11.6 – 15.9)	13.90 (7.9 – 17.4)	0.195
WBC, $\times 10^9$ cells/L	9.75 (5.78 -17.25)	6.70 (2.36 – 15.98)	0.001
Neutrophil count			
Absolute, $\times 10^9$ cells/L	8.11 (4.53 – 15.50)	3.99 (1.99 – 13.78)	<0.001
Relative, %	84.05 (73.60 – 95.20)	60.60 (40.20 – 93.50)	<0.001
Lymphocyte count			
Absolute, $\times 10^9$ cells/L	0.70 (0.31 – 1.53)	1.64 (0.31 – 5.92)	<0.001
Relative, %	10.20 (3.0 – 14.20)	26.40 (1.29 – 53.60)	<0.001
Monocyte count			
Absolute, $\times 10^9$ cells/L	0.55 (0.05 – 1.15)	0.57 (0.09 – 1.66)	0.031
Relative, %	6.10 (0.70 – 14.2)	8.90 (0.32 – 25.00)	0.011
Platelet count, $\times 10^9$ cells/L	267 (122 – 446)	235 (54 – 672)	0.448
LMR	1.49 (0.37 – 6.20)	2.98 (0.44 – 9.66)	0.001

if p<0.05. SPSS software version 25.0 was used for all statistical analyses.

RESULTS

A total of 502 subjects were involved in this study. 71.5% of patients in the non-survivors group had an underlying disease. There are significant differences in LMR values in the survivors group compared to non-survivors (Table 1).

Using ROC analysis, we obtained a cut-off value of LMR less than 2.0 to predict the occurrence of death in hospitalized COVID-19 patients (Graph 1 and Table 2).

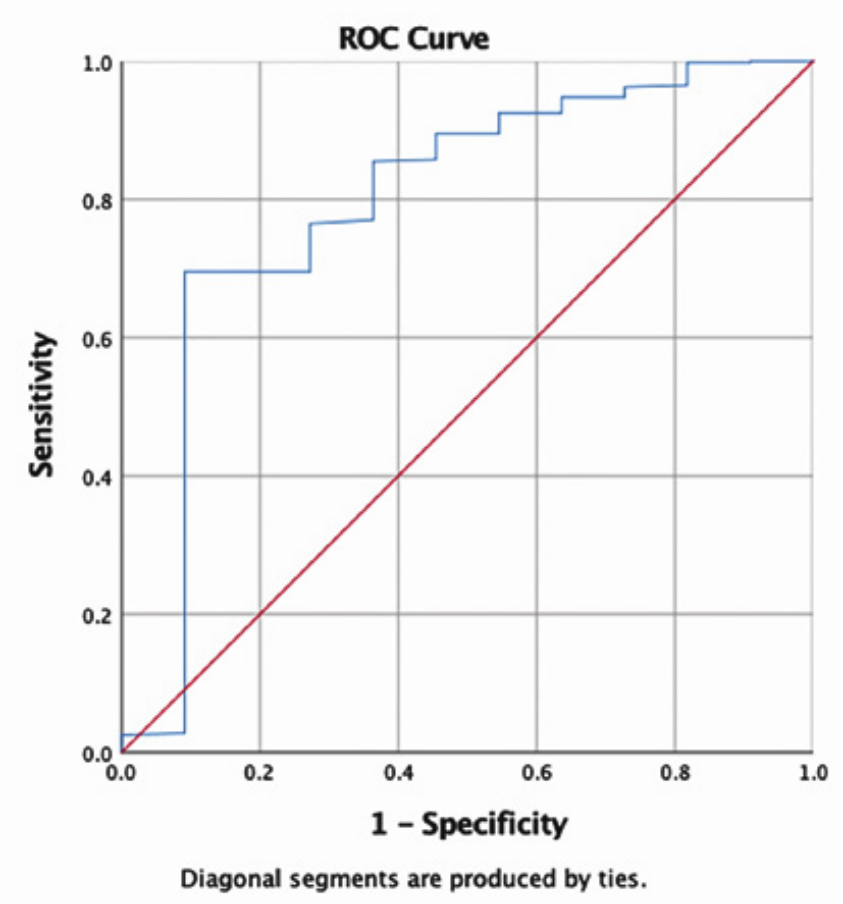
By including the variables age and presence of underlying disease in multiple logistic regression analysis, we obtained an adjusted odds ratio (OR) of LMR of 3.62 (95% CI 1.92-14.25; p=0.046) (Table 3).

DISCUSSION

We found a significant association between LMR and survival in COVID-19. This association remained significant after the

Table 2. Cut-off values, sensitivity, specificity, and AUC of LMR

	Cut-off value	Sensitivity	Specificity	Area under curve	95% confidence interval	p-value
LMR	<2.0	76.5%	72.7%	0.797	0.639 – 0.956	0.001



Graph 1. ROC analysis of the LMR variable

Table 3. Crude odds ratio and adjusted odds ratio of LMR, age, and underlying disease

	Odds ratio	95% confidence interval	P value	Adjusted odds ratio	95% confidence interval	P value
LMR	8.62	2.24 - 33.14	0.002	3.62	1.92 – 14.25	0.046
Age	5.15	1.59 - 16.69	0.006	1.77	1.29 – 11.03	0.038
Underlying disease	7.11	2.03 - 24.89	0.002	5.17	1.19 – 22.43	0.028

LMR: Lymphocyte-to-monocyte ratio

multivariate analysis included age and underlying disease variables. COVID-19 is a disease with systemic multiorgan disorders caused by SARS-CoV-2. The inflammatory mediators release can increase the activation of the immune system, which causes an inflammatory storm and tissue damage[7]. Inflammatory biomarkers can predict disease severity and assess therapy's effectiveness.

SARS-CoV-2 causes a decrease in the number of lymphocytes in infected patients. Lymphocyte apoptosis due to immune-mediated mechanisms or direct viral effects on lymphocytes is the pathogenesis leading to lymphopenia[12]. Lymphocytes and monocytes are essential in the inflammatory cascade of COVID-19 infection. Studies show that in COVID-19 infection, the lymphocyte ratio is a better predictor for assessing the severity of infection than the total leukocyte count[13].

Monocytes can be an excellent marker to assess the severity of infection in COVID-19 patients. Studies show that monocyte counts are higher in COVID-19 patients compared to flu patients[14]. Monocytes are essential in phagocytosis, antigen presentation, and inflammatory response[15]. The study by Zhou et al. in severe COVID-19 shows a significant increase in monocytes that produce interleukin-6 in the peripheral blood, indicating that monocytes have a significant role in the occurrence of cytokine storms[16]. Lower LMR values are associated with severe clinical symptoms and the need for mechanical ventilation in COVID-19 patients[11,16].

LMR can be easily calculated from a complete blood count, provides fast results, is cheap, and is available in all health facilities, including areas with limited resources. Identification of patients at high risk at early onset of the disease is critical so that appropriate and aggressive therapy can be given to prevent complications and death.

This study is a retrospective cohort with a relatively large sample size. The limitation of this study is that it did not record the pattern of changes in LMR values and was a single-center study.

CONCLUSIONS

Lymphocyte-to-monocyte ratio is significantly lower in non-survivors. LMR can reflect the disease severity and will assist clinicians in identifying patients at risk for complications and death. More studies are needed to confirm these findings.

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Ethical approval

This study has received ethical clearance from the Research Ethics Committee of the Faculty of Medicine, Udayana University (ethical approval number 1010/UN14.2.2.VII.14/LT/2020).

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Conflict of interest disclosure

The authors declare that there are no conflicts of interest.

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