Indonesian Journal of Medical Laboratory Science and Technology

Open Access p-ISSN 2684-6748 | e-ISSN 2656-9825 IJMLST

Neutrophil-Lymphocyte Ratio (NLR) and Lymphocyte-Monocyte Ratio (LMR) as Covid-19 Screening Parameters

Heny Syahrini[1], Trinugroho Heri Fadjari[2], Nadjwa Zamalek Dalimoenthe[3]

[1]Haematology and Medical Oncology Division, Internal Medicine Departement, Universitas Sumatera Utara, Medan, Indonesia

[2]Haematology and Medical Oncology Division, Internal Medicine Departement, Hasan Sadikin Hospital, Bandung, Indonesia

[3]Clinical Pathology Departement, Hasan Sadikin Hospital, Bandung, Indonesia

Correspondence:
Heny Syahrini,
Jln. Bunga Lau No.17 Medan North Sumatra, Indonesia
Zip Code: 20136

Email: henylubis01@gmail.com

Received: August 21, 2021
Revised: October 23, 2021
Accepted: January 1, 2022
Published: April 28, 2022

DOI: 10.33086/ijmlst.v4i1.2281

Abstract

Coronavirus Disease 2019 (COVID-19) diagnosis generally uses RT-PCR as the gold standard to detect coronavirus-2 (SARS-CoV-2); however, this method requires advanced laboratory equipment. Alternatively, Neutrophil-Lymphocyte Ratio (NLR) and Lymphocyte-Monocyte Ratio (LMR) can be used to identify viral infection. The study aimed: (1) to compare each NLR and LMR ratio in patients with and without COVID-19 and (2) to test the effectiveness of these ratios in identifying COVID-19. The study was conducted at the Haji Adam Malik Central General Hospital, Medan, Indonesia by acquiring 87 medical records data. The complete hematologic profile was analyzed from patients with and without COVID-19. The NLR and LMR ratio accuracy were analyzed as a screening tool for COVID-19. The AUC of NLR was 0.638, with cut-off ≤ 2.49, 47.6% sensitivity, and 80% specificity; therefore, the NLR accuracy as a screening for COVID-19 was defined as not good (just sufficient) because of AUC <0,7. The AUC of LMR was 0.661, with cut-off ≥ 3.23, 45.2% sensitivity, and 82.2% specificity; therefore, the LMR accuracy as a screening parameter for COVID-19 is defined as not good (just sufficient) because of AUC <0,7. There were significant differences in hematologic profile in neutrophil, lymphocyte, NLR, LMR between the patients in the COVID-19 group and non-COVID-19 group. NLR and LMR cannot be used as a screening tool because the Area Under Curve (AUC) is not good enough (just sufficient) in detecting COVID-19.

Keywords

COVID-19, Neutrophil-Lymphocyte Ratio, Lymphocyte-Monocyte Ratio.

INTRODUCTION

The world went into chaos around December 2019 when a new virus outbreak emerged in Wuhan, China. This virus spread into every corner of the world; therefore World Health Organization (WHO) stated coronavirus diseases 2019 (COVID-19) as a pandemic that is caused by a virus entity named Severe Acute Respiratory Syndrome Corona Virus-2 (SARS-CoV-2) (1,2).

The clinical manifestations of COVID-19 consisted of mild symptoms (e.g., fever, cough, myalgia, fatigue, and diarrhea) and severe symptoms (e.g., life-threatening dyspnea, respiratory failure, coagulation disturbance, headache, loss of consciousness, hemoptysis, multiorgan failures, and even death) (3,4). Several parameters that describe severe clinical manifestations are respiratory rate >30 times/minute, oxygen saturation below 93%, the ratio of oxygen partial gas pressure and oxygen inspiration fraction <300 mmHg (PaO_2/FiO_2 <300), and infiltrates on lung X-ray increasing more than 50% in 24 to 48 Hours (5).

Early detection and screening should be conducted for every patient that needs medical attention at every hospital or medical center. A patient classified as a suspect or probable COVID-19 must undergo gold standard Real-Time Polymerase Chain Reaction (RT-PCR) to detect SARS-CoV-2 virus nucleic acid in the sputum, an oropharyngeal and nasal swab of the patient (6,7). However, RT-PCR often shows late results, as it needs complex procedures, many samples, and a highly advanced laboratory workplace. RT-PCR is less efficient to use as a screening method by several considerations; however, this method remains the gold standard in diagnosing COVID if the equipment is adequate (6).

Neutrophil-Lymphocyte Ratio (NLR) is a ratio of absolute neutrophil count to absolute lymphocyte count. This value can be easily calculated according to findings from routine hematology profiles. It is reported that this ratio has an impactful effect on inflammation in the patient. Peripherally acquired samples of blood also can be used to calculate this ratio. This ratio is also beneficial in determining the cause of the infection, such as described in a retrospective study where a high ratio value indicates a bacterial infection in a fever of unknown origin (8,9). Lymphocyte-monocyte ratio (LMR) can also be used to identify viral infection in a human. A ratio < 2 according to one study can be applied to diagnosing influenza infection instead of the standard rapid test (10).

These ratios are even more convenient to use in COVID cases as the percentage of leukocytes, lymphocytes, and neutrophils are greatly affected by the SARS-CoV-2 virus. Compared to an unaffected person, a person

with COVID-19 has much lower leukocyte and lymphocyte counts and much higher neutrophil counts. One study shows that a COVID-19 patient may have leucopenia with 2,91 x 10^9/L, with 70% neutrophils (11). Another study shows that the NLR ratio is significantly lower in COVID-19 patients. The absolute leukocyte, lymphocyte, and monocyte counts are much lower than non-COVID-19 patients (12). The severity of COVID-19 is also distinguished according to the ratio where the NLR ratio is higher in severe COVID-19, while the LMR ratio is lower in less severe COVID-19 infection (12,13). Although promising, these ratios have not been fully utilized yet as more precise data are needed to further evaluate the effectiveness of these ratios as sensitive and specific screening tools for COVID-19.

The study aims of this study are to compare each NLR and LMR ratio in patients with COVID-19 and without COVID-19 in severe and less severe COVID-19 infection and (2) to test these ratios' effectiveness in identifying COVID-19.

MATERIALS AND METHODS

Study Population

The study was conducted at the Haji Adam Malik Central General Hospital, Medan cityt approved by the Research Ethics Committee, Faculty of Medicine, Universitas Sumatera Utara (No. 252/TGL/KEPK FK USU-RSUP HAM/2020). The population of this study is patients categorized as probable of COVID-19. This study was conducted from April 2020 until June 2020. The subjects of this study are patients categorized as definitive COVID-19 with the positive result of RT-PCR SARS-CoV-2. We gathered secondary medical records and collected the hematologic profile of patients categorized as probable COVID-19. The patients older than 18 and confirmed COVID-19 by RT-PCR were included. Patients younger than 18 years old and still categorized as probable COVID-19 were excluded.

Medical Record Data

This study used secondary data (the medical record of the patients) with parameters including the number of medical records, age, sex, RT-PCR result, severity, primary diagnosis, additional diagnosis, the endpoint of the patients, full hematologic profile (hemoglobin, leukocyte, thrombocyte, total leukocyte count: eosinophil, basophil, band neutrophil, segmented neutrophil, lymphocyte, monocyte), procalcitonin, and chief complaint.

Operational Definition

Probable COVID-19 is defined as subjects seeking medical attention with symptoms related to COVID-19. COVID-19 Confirmed defined as patients with the positive result of RT-PCR. Severe COVID-

19 is defined as patients confirmed with COVID-19 who had one of these criteria: respiratory rate more than 30 times/minute; Oxygen saturation < 93%, PaO_2/FiO_2 < 300 mmHg. Less Severe COVID-19 is defined as confirmed COVID-19 without severe COVID-19 criteria. Neutrophil and Lymphocyte Ratio is the ratio of absolute neutrophil count to absolute lymphocyte count, acquired by analyzing peripheral blood smear prepared on the day of the admission into the hospital. Lymphocyte and Monocyte Ratio is defined as the ratio of absolute lymphocyte count to absolute monocyte count, acquired by analyzing peripheral blood smear, prepared on the day of the admission into the hospital.

Statistical analyses

All data were analyzed using SPSS Version 11.0 Statistics for Windows software. The baseline characteristics of the study population were presented in descriptive distribution tables. Data are presented as mean ± standard deviation (SD) or n (%).

Data analysis was conducted by unpaired T-test if the data had a normal distribution. If the data were unevenly distributed, data analysis was conducted by the Mann-Whitney test. To evaluate NLR and LMR ratios as a screening method for COVID-19, we used parameters sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and area under the curve (AUC) from the receiver operating curve (ROC). AUC value 0.9-1 categorized as exceedingly accurate, 0.8-0.9 categorized as highly accurate, 0.7-0.8 categorized as well accurate, 0.6-0.7 categorized as fairly accurate, and < 0.5 categorized as useful.

RESULTS

There were 87 data of medical records from patients (18 – 71 years old) included in this study. There were 52 male patients (59.8%) and 35 female patients (40.2%), 21 female and 21 male in the COVID-19 group, and 31 male and 14 female in the non-COVID-19 group. There were no statistically significant differences in the hemoglobin, leukocyte, thrombocyte, eosinophil, basophil, neutrophil, and monocyte amount in COVID-19 and non-COVID-19. However, the median of the lymphocyte in the COVID-19 group (1.4%-57.7%, average: 19.8%) was higher than lymphocyte in the non-COVID-19 group (1.8%-46.4%, average: 15.7%), and this was statistically significant with a p-value of 0.016 ($p<0.05$). The median of the absolute neutrophil count in the COVID-19 group (2,250.00–14,297.22, average: 5,471.77) was lower than in the non-COVID-19 group (1,170.78–47,329.25, average: 7756,56), and this was statistically significant, with a p-value of 0.0007 ($p<0.05$).

There were no significant differences in severity, endpoint, comorbidity, and duration

of complaint in the COVID-19 group compared to the non-COVID-19 group. The symptoms of fever and cough were more prevalent in the COVID-19 group than the non-COVID-19 group, and this was statistically significant, P-value 0.004 for fever and 0.008 for cough. There were no significant differences in comorbidity between the COVID-19 group and the non-COVID-19 group.

Table 1. Baseline Characteristic

Variable	Total (n=87) median (range)	COVID-19 (n=42) median (range)	Not COVID-19 (n=45) median (range)	P-value*
Age (year)	44 (18-71)	43 (18-71)	48 (19-71)	0.637[a]
Sex				
Male, n (%)	52 (59.8)	21 (50.0)	31 (68.9)	0.073[b]
Female, n (%)	35 (40.2)	21 (50.0)	14 (31.1)	
Hematologic Parameters				
Hemoglobin	12.9 (5.8-17.4)	13.2 (5.8-17.1)	12.7 (6.4-17.4)	0.997[a]
Leukocyte	9,130 (2,370-49,250)	8,475 (4,010-16,200)	10,060 (2,370-49,250)	0.070[a]
Thrombocyte ($x10^3$)	282 (32-644)	274 (46-600)	283 (32-644)	0.728[a]
Eosinophil (%)	0.8 (0.0-8.2)	0.8 (0.0-6.0)	0.8 (0.0-9.2)	0.547[a]
Basophil (%)	0.3 (0.0-9.2)	0.3 (0.0-1.1)	0.3 (0.0-9.2)	0.188[a]
Neutrophil (%)	73.7 (33.9-96.1)	68.7 (33.9-95.8)	75.6 (40.7-96.1)	0.058[a]
Limphocyte (%)	17.0 (1.4-57.5)	19.8 (1.4-57.7)	15.7 (1.8-46.4)	**0.016[a]***
Monocyte (%)	7.0 (0.7-18.0)	7.0 (2.7-15.4)	7.5 (0.7-18.0)	0.792[a]
Absolute neutrophil	6,232.54 (1,170.78-47,329.25)	5,47177 (2,250-14,297.22)	7,756.56 (1,170.78-47,329.25)	**0.007[a]***
Absolute limphocyte	1,693.2 (201.32-5,158.38)	1,843.02 (421.80-5,158.38)	1,377.88 (201.32-4,538.4)	0.159
Absolute monocyte	690.2 (170.8-3,145.5)	572.77 (312.9-1,328.1)	701.1 (170.8-3,145.5)	0.114
Severity				
Severy	18 (20.7)	10 (23.8)	8 (17.8)	0.488[b]
Less Severe	69 (79.3)	32 (76.2)	37 (82.2)	
Endpoint				
Death	22 (25.3)	11 (26.2)	11 (24.4)	0.851[b]
Cured	65 (74.7)	31 (73.8)	34 (75.6)	
Comorbidity, n (%)				
None	64 (73.6)	27 (64.3)	37 (82.2)	0.356[b]
DM	13 (14.9)	9 (21.4)	4 (8.9)	
ESRD	4 (4.6)	3 (7.1)	1 (2.2)	
Sepsis	4 (4.6)	2 (4.8)	2 (4.4)	
HIV	2 (2.3)	1 (2.4)	1 (2.2)	
Duration of Complaint				
≤14 days	59 (84.3)	29 (82.9)	30 (85.7)	0.743[b]
>14 days	11 (15.7)	6 (17.1)	5 (14.3)	
Symptoms				
Fever, n (%)	46 (52.9)	29 (69.0)	17 (37.8)	**0.004[b]***
Cough, n (%)	37 (42.5)	24 (57.1)	13 (28.9)	**0.008[b]***
Dyspneu, n (%)	33 (37.9)	13 (31.0)	20 (44.4)	0.195[b]
Dysphagia, n (%)	6 (6.9)	3 (7.1)	3 (6.7)	1.000[c]
Others, n (%)	9 (10.3)	4 (9.5)	5 (11.1)	1.000[c]

P-value measured using [a] Mann Whitney test, [b] Chi-square test, [c] Fisher Exact test; * significant if p <0.05

There were 42 patients in the COVID-19 group, about ten patients categorized as severe COVID-19 group, and 32 patients categorized as less severe COVID-19 group

(Table 1). The median age in the COVID-19 group was 43 years (range: 18 – 71), and the median age in the severe group was 54 (range 28 – 69) and 36.5 (range 18-71) in the less severe group. This was statistically significant with P-value of 0.026 ($p < 0.05$). The severe COVID-19 group consisted of older patients. The hematologic parameters, like hemoglobin, leukocyte, monocyte, had no significant differences in COVID-19 and non-COVID-19 groups.

However, for other parameters, there are some statistically significant differences. The median of thrombocytes ($x10^3$) was 223.5 in the severe COVID-19 group and 295.5 in the less severe group. This study showed that patients with severe COVID-19 had a lower median of thrombocyte than less severe COVID-19 (p-value 0.045) (Table 2).. The median of eosinophil was 0.75 (0.0-6.0) in overall COVID-19 patients, 0 (0-2.9) in the severe COVID-19 group and 1.2 (0-6) in less severe COVID-19 group. This study showed that patients with severe COVID-19 had a lower median of eosinophil than less severe COVID-19, p-value 0.001.

Table 2. The Hematologic profile of severe COVID-19 group and not severe COVID-19 group

Variable	Total (n=42) median (range)	Severity of COVID-19		P-value
		Severe (n=10) median (range)	Not Severe (n=32) median (range)	
Age (Years)	43 (18-71)	54 (28-69)	36.5 (18-71)	**0.026[a]***
Sex				
Male, n (%)	21 (50)	6 (60)	15 (46.9)	0.174[b]
Female, n (%)	21 (50)	4 (40)	17 (53.1)	
Hematologic Parameters				
Hemoglobin	13.2 (5.8-17.1)	11.95 (6.0-15.5)	13.4 (5.8-17.1)	0.231[a]
Leukocyte	8,475 (4,010-16,200)	10,265 (4,010-16,200)	8,370 (5,000-16,000)	0.535[a]
Thrombocyte (x1000)	274.0 (46.0-600.0)	223.5 (76.5-318.0)	295.5 (46-600)	**0.045[a]***
Eosinophil (%)	0.75 (0.0-6.0)	0 (0-2.9)	1.2 (0-6)	**0.001[a]***
Basophil (%)	0.25 (0.0-1.1)	0.1 (0-0.6)	0.4 (0-1.1)	**0.003[a]***
Neutrophil (%)	68.7 (33.9-95.8)	79.35 (74.9-92.1)	60.1 (33.9-95.8)	**0.001[a]***
Limphocyte (%)	19.8 (1.4-57.7)	12.6 (4.8-17.4)	29.4 (1.4-57.7)	**0.001[a]***
Monocyte (%)	6.9 (2.7-15.4)	6.95 (3.1-11)	7 (2.7-15.4)	0.636[a]
Absolute neutrophil	5,471.77 (2,250-14,297.22)	6,489.76 (3,845.4-13,867.2)	5,224.92 (2,250-14,297.22)	0.111
Absolute lymphocyte	1,843.02 (421.8-5,158.38)	1,218.19 (421.8-2,001.6)	2,219.78 (529.32-5,158.38)	**0.012***
Absolute monocyte	572.77 (312.9-1,328.1)	523.47 (356.81-1,159.26)	596.41 (312.9-1,328.1)	0.859

P-value measured using [a] Mann Whitney test, [b] Chi-square test, [c] Fisher Exact test * significant if p <0.05

The median of basophil was 0.25 (0.0-1.1) in overall COVID-19 patients, 0.1 (0-0.6) in the severe COVID-19 group and 0.4 (0-1.1) in less severe COVID-19 group. This

study showed that patients with severe COVID-19 had a lower median of basophil than less severe COVID-19, p-value 0.003. The median of neutrophils was 68.7 (33.9-95.8) in overall COVID-19 patients, 79.35 (74.9-92.1) in the severe COVID-19 group, and 60.1 (33.9-95.8) in the less severe COVID-19 group. This study showed that patients with severe COVID-19 had a higher median of neutrophil than less severe COVID-19, p-value 0.001.

The median of neutrophils was 68.7 (33.9-95.8) in overall COVID-19 patients, 79.35 (74.9-92.1) in the severe COVID-19 group 60.1 (33.9-95.8) in the less severe COVID-19 group. This study showed that patients with severe COVID-19 had a lower median of neutrophil than less severe COVID-19, p-value 0.001. The median of absolute lymphocyte count was 1,843.02 (421.8-5,158.38) in overall COVID-19 patients, 1,218.19 (421.8-2,001.6) in the severe COVID-19 group and 2,219.78 (529.32-5,158.38) in less severe COVID-19 group. This study showed that patients with severe COVID-19 had a lower median absolute lymphocyte count than less severe COVID-19, p-value 0.012.

The median of NLR in the COVID-19 group (0.59-68.43, average: 3.55) was lower than the non COVID-19 group (0.97-53.39, average: 4.75), and this was stastitically significant with p-value 0.027 ($p < 0.05$) (Table 3).. The median LMR ratio in th COVID-19 group (0.52-16.49, average: 28.5) was higher than non COVID-19 group (0.36-9,87, average: 2.01). This was statistically significant with p-value 0.010 ($p < 0.05$).

Table 3. NLR and LMR value in COVID-19 and non COVID-19

Variable	Total (n=90) median (range)	COVID-19 (n=43) median (range)	Non COVID-19 (n=47) median (range)	P-value
NLR	4.35 (0.59-68.43)	3.55 (0.59-68.43)	4.75 (0.97-53.39)	**0.027***
LMR	2.26 (0.36-16.49)	2.85 (0.52-16.49)	2.01 (0.36-9.87)	**0.010***

P value calculated using Mann-Whitney test*significant if p-value < 0.05

The median NLR ratio in the COVID-19 group with severe category (4.30-19.19, average: 6.20) was lower than in the non-COVID-19 group (5.27-53.39, average: 13.59). However, this result was statistically insignificant because of the p-value of 0.110 ($p>0.05$) (Table 4). The median NLR in the non-severe COVID-19 group was 2.00 (0.59-68.53). This value was lower than in the non-COVID-19 group 4.26 (0.97-19.74), with a p-value of 0.01 ($p < 0.05$). P value of less than 0.05 can be interpreted statistically significant.

The median LMR ratio in the severe COVID-19 group (1.04-3.36, average: 1.77) was higher than the non-COVID-19 group (0.73-2.52, 1.19). However, this result is defined ad statistically insignificant as the p-value is 0.131 (p > 0.05). The median LMR ratio was 3.47 (0.52-16.49). This value was lower when compared to the non-COVID-19 group compared with control 2.11 (0.36-9.87). This result was statistically significant with a p-value of 0.008 (p<0.05).

Table 4. The NLR and LMR ratio in COVID-19 patients and non COVID-19 patients based on the severity

Variable	Severe Cases			Not Severe Cases		
	COVID-19 (n=10) median (range)	**Not COVID-19 (n=8) median (range)**	**P-value**	**COVID-19 (n=32) median (range)**	**Not COVID-19 (n=37) median (range)**	**P-value**
NLR	6.20 (4.30-19.19)	13.59 (5.27-53.39)	0.110	2.00 (0.59-68.43)	4.26 (0.97-19.74)	**0.010***
LMR	1.77 (1.04-3.36)	1.19 (0.73-2.52)	0.131	3.47 (0.52-16.49)	2.11 (0.36-9.87)	**0.008***

P-value calculated using Mann-Whitney test*significant if P-value < 0.05

The median NLR of the severe COVID-19 group was 6.20 (4.30-19.19), higher than the less severe COVID-19 group 2.00 (0.59-68.43). With p-value 0.001 (p < 0.05), this result was statistically significant. The median LMR ratio of the severe COVID-19 group was 1.77 (1.04-3.36), lower than the less severe COVID-19 group 3.47 (0.52-15.49). With p-value 0.003 (p < 0.05), this result was statistically significant (Table 5).

Table 5. The NLR and LMR ratio in severe COVID-19 patients and less severe COVID-19 patients

Variable	Severity		P value
	Severe (n=10) median (range)	**Less Severe (n=32) median (range)**	
NLR	6.20 (4.30-19.19)	2.00 (0.59-68.43)	**0.001***
LMR	1.77 (1.04-3.36)	3.47 (0.52-16.49)	**0.003***

P-value calculated using Mann-Whitney test *significant if p-value < 0.05

The accuracy of the NLR parameter was defined as not good (just sufficient) because of AUC < 0.7 (cut-off value ≤ 2.49, AUC 0.638, sensitivity 47.6%, and specificity 80%) (Table 6). The LMR value, with a cut-off LMR ≥ 3.23, AUC 0.661, sensitivity: 45.2%, specificity: 82.2%, the accuracy of the LMR parameter as a screening for COVID-19 cases also defined as not good (only sufficient) because of AUC < 0.7.

DISCUSSION

The number of leukocytes in the COVID-19 group was lower than in the non-COVID-19 group, based on the baseline characteristics of the study subjects. However, in this study, the difference was not significant (8,475 [4,010- 16,200] vs 10,060 [2,370- 4,9250], p = 0.070). This study is in line with previous studies by Mardani et al. (11) and Song CY et al. (13). However, in both of these studies, the difference in leukocytes was indicated statistically significant differences.

Tabel 6. *Cut-off* of AUC NLR dan LMR ratio as a screening tool for COVID-19

Variable	AUC	95% CI	P value	Cut-off	
NLR	0.638	0.528-0.738	0.022	≤2.49	Sensitivity: 47.6% Specificity: 80.0% PPV: 69.0% NPV: 62.1%
LMR	0.661	0.552 – 0.759	0.006	>3.23	Sensitivity: 45.2% Specificity: 82.2% PPV: 70.4% NPV: 61.7%

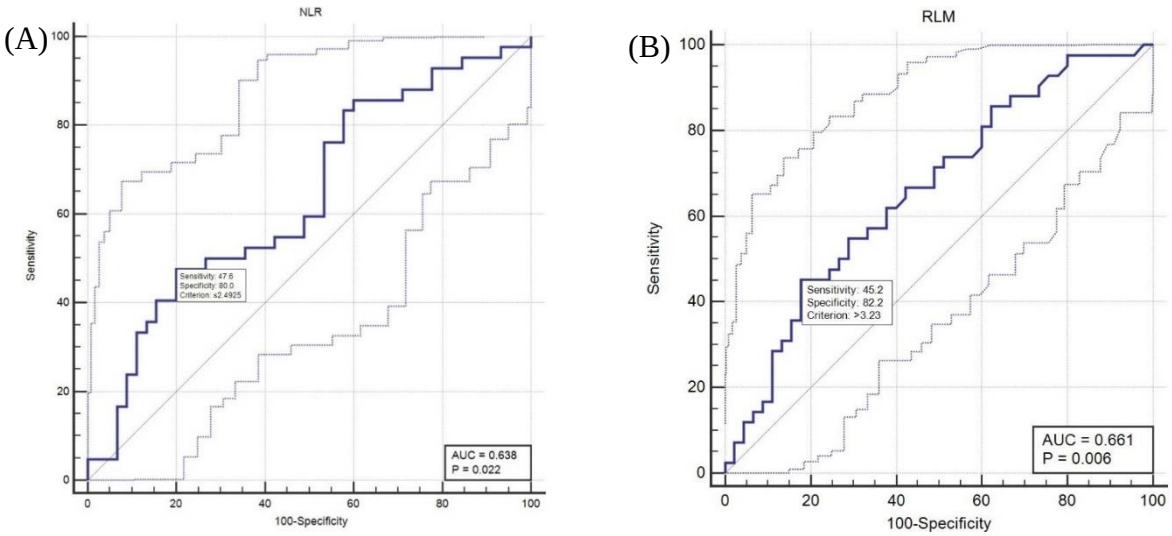

Figure 1. ROC Curve (A) NLR on Covid-19 (B) LMR on Covid-19

This study also found that approximately 75% of COVID-19 cases were not severe, with relatively younger age in less severe cases than severe cases (median age 36.5 versus 54 years).

The following baseline characteristic is the discovery of lymphopenia in both groups, both in COVID-19 and non-COVID-19 groups. Previous studies stated that lymphopenia is often found in COVID-19 patients. Lymphopenic conditions have been discovered to be common, especially in severe COVID-19 patients, due to a variety of mechanisms, including direct lymphocyte

inhibition, lymph node destruction, inflammatory cytokines, the emergence of lactic acidosis suppression lymphocytes, and attachment of coronavirus to Angiotensin-converting enzyme 2 (ACE) 2 receptors on lymphocytes (14).

The difference in lymphocyte percentages between the COVID-19 and non-COVID-19 patient groups is quite significant, with the median lymphocyte value in the COVID-19 group significantly higher than the non-COVID-19 group (median values 19.8 [1.4-57.7] vs. 15.7 [1.8-46.4], p 0.016). Although the absolute lymphocyte count in the COVID-19 group was higher than the non-COVID-19 group (1843.02 [421.8-5158.38] vs. 1377.88 [201.32-4538.4], the difference was not statistically significant. In addition, the cycle threshold from the positive RT-PCR SARS CoV-2 results might further explain why the COVID-19 group has the absolute median value of lymphocytes that are still normal (1843.02 [421.8-5158.38]), with no lymphopenia. The SARS CoV-2 positive RT-PCR results with high cycle threshold results indicate low viral loads. The RT-PCR cycle threshold ≤ 29 indicates the amount of viral nucleic acid tested is enormous and vice versa if the cycle threshold value ≥ 30 indicates the minimum to moderate amount of viral nucleic acid tested (16). Viral load measurements from samples tissue indicate an active viral replication. They can be routinely monitored for severe viral respiratory tract infections, including clinical progression, response to treatment, healing, and recurrence (17). Increasing severity is also associated with the presence of lymphopenia (15). Thus, if the lymphocytes count has a normal range, the condition is probably associated with less viral load and a higher cycle threshold value (≥30). Unfortunately, this study's SARS-CoV-2 positive RT-PCR examination did not include the cycle threshold value. In addition, in this study, it was found that the RT-PCR group of SARS-CoV-2 negative experienced lymphopenia. This condition, characterized by a decrease in lymphocyte value, can be explained by comorbidities such as diabetes mellitus, sepsis, human immunodeficiency virus, and end-stage renal disease (18,19).

The data on baseline characteristics in this study also showed that the percentage of neutrophils, absolute neutrophils, monocytes, and the absolute monocytes in the COVID-19 group was lower than that in the non-COVID-19 group, with only the absolute neutrophils statistically significant (5471.77 [2250-14297.22] vs. 7756.56 [1170.78-47329.25], p = 0.007).

In another study, Mardani et al. (11) presented different results, that the percentage of neutrophils in the COVID-19 group was significantly higher than in the non-COVID-19 group. Phagocytic cells such as dendritic cells, macrophages/monocytes,

and neutrophils play an essential role in the presence of SARS-CoV virus infection. In addition to airway epithelial cells and NK cells, it is also said that SARS-CoV-2 can infect monocyte immune cells and circulating T lymphocytes in the early stages of the disease. The infection rate in lymphocytes was 51.9% and 27.9% in monocytes. Monocytes and T cells are involved in the innate and adaptive immune systems. The destruction of these cells can result in a compromised immune response (20). The decrease in monocyte value is associated with the destruction of these monocyte cells.

The characteristic data also found that the types of complaints often found in COVID-19 cases were fever (69%) and cough (57.1%), and these complaints were significantly different from non-COVID-19 cases.

In this study, between the COVID-19 group with severe and less severe symptoms, the percentage of neutrophils and the absolute value of neutrophils in the severe group was higher than in the less severe group. However, statistically, the significant value was only in the percentage of neutrophils (median value of 79.35 [74.9-92.1] vs 60.1 [33.9-95.8], p = 0.001).

The percentage of monocytes in the study was also not significantly different between the severe and non-severe COVID-19 groups (median value of 6.95 [3.1-11] vs. 7 [2.7-15.4], p = 0.636). For the absolute value of monocytes in this study, the severe COVID-19 group had a lower absolute monocyte value than the non-severe group. However, this difference was not significant (523.47 [356.81-1159.26] vs 596.41 [312.9-1328.1], p = 0.859).

The NLR result in the COVID-19 group was lower than the non-COVID-19 group (median value 3.55 [0.59-68.43] vs 4.75 [0.97-53.39], p = 0.027). In the severe symptom group, the NLR value was lower in COVID-19 compared to non-COVID-19, but this difference was not significant (median 6.20 [4.30-19.19] vs. 13.59 [5.27-53.39], p = 0.110). In the moderate symptom group, the NLR value was significantly lower between COVID-19 and non-COVID-19 (median 2.00 [0.59-68.43] vs 4.26 [0.97-19.74] , p = 0.01). This result is inversely proportional to the previous study conducted by Mardani et al. (11), which showed a higher percentage of neutrophils and a lower percentage of lymphocytes in the COVID-19 group than in the non-COVID-19 group so that in the end, the NLR value was higher in the COVID-19 group than in the non-COVID-19 group. The NLR results were different in severe and non-severe COVID-19. NLR in severe COVID-19 group was significantly higher than those in the moderate-grade group (6.20 [4.30-19.19] vs 2.00 [0.59-68.43], p = 0.001). This result is in line with the research of Yang Ap et al. (2020) and Song CY et al. (2020), who stated that the NLR in severe COVID-19 was

significantly higher than those that were not severe.

The LMR value in the COVID-19 group was higher than the non-COVID-19 group. This study also compared LMR based on the degree of disease severity between COVID-19 and non-COVID-19. In the severely ill group, there was no significant difference in LMR between COVID-19 and non-COVID-19 (median 1.77 [1.04-3.36] vs 1.19 [0.73-2.52], p = 0.131). When the LMR ratio of the less severe COVID-19 group was compared to the non-COVID 19 groups, the LMR ratio was higher in the severe COVID-19 group, median 3.47 (0.52-16.49) vs. 2.11 (0.36-9.87), p = 0.008.

There was no previous research comparing the LMR value between the COVID-19 and non-COVID-19 groups that has been published, so the results of this study provide new information for COVID-19 cases. The results of the LMR in this study for severe degrees of COVID-19 were significantly lower than the non-severe group (1.77 [1.04-3.36] vs. 3.47 [0.52-16.49], p = 0.003).

The NLR and LMR values were studied to find their accuracy as screening parameters for COVID-19 cases. NLR AUC was 0.638, with a cut-off of ≤2.49, 47.6% sensitivity, and 80% specificity; therefore, the accuracy of the NLR parameter as a screening for COVID-19 cases is defined as not good enough (only sufficient) because of AUC <0.7.

In a previous study, Song CY et al. (2020) used a cut-off >5.8 as one of the assessment parameters to determine cases of COVID-19 along with other parameters made in the form of a COVID-19 early detection score.

A cut-off value of ≥3.3 indicates a COVID-19 patient presenting with less severe symptoms will develop into a severe condition as much as 46.1% within 6.3 days. Conversely, the cut-off of ≤3.3 indicates that COVID-19 patients with non-severe symptoms will experience improvement and be outpatient within 13.5 days (13). LMR AUC was 0.661, with cut-off ≥3.23, 45.2% sensitivity, 82.2% specificity; therefore, the accuracy of the LMR parameter as a screening for COVID-19 cases is defined as not good enough (just sufficient) because of AUC <0.7.

Previous research regarding LMR parameters as filter parameters for COVID-19 is not available. Previous studies related to LMR parameters in COVID-19 were prognostic studies to assess the clinical outcome of COVID-19 patients. Yang AP et al. (2020) explained that the LMR could not be used as a good prognostic parameter in the case of COVID-19 because the AUC value obtained is around 0.265 (AUC <0.5).

Several comorbidities were not excluded from this study's samples, affecting the

results. The research data obtained only from one of the hospitals is one of the limitations of this study.

We recommended that future studies focus on searching for better and newer COVID-19 screening tools with high sensitivity and specificity, cheap, easy, and non-invasive.

CONCLUSIONS

There were significant differences in hematologic profile in neutrophil, lymphocyte, NLR, and LMR between the COVID-19 and non-COVID-19 groups. Nevertheless, NLR and LMR cannot be used as screening tools because the Area Under Curve (AUC) is not good enough in detecting COVID-19.

AUTHOR CONTRIBUTIONS

HS had full access to all the data and took responsibility for the integrity of the data and the accuracy of the data analysis.

HS and THF contributed to the concept and design of the study

HS and NZD contributed to the critical revision of the manuscript for important intellectual content and statistical analysis

All authors contributed to data acquisition, analysis, or interpretation and reviewed the final manuscript.

ACKNOWLEDGMENTS

The authors thank colleagues from Universitas Padjajaran (Division of Haematology and Medical Oncology, Faculty of Medicine), Hasan Sadikin General Hospital, Universitas Sumatera Utara (Faculty of Medicine), and Haji Adam Malik General Hospital for providing insight, assistance, and expertise for authors.

We thank Dr. Rico Andryan Simatupang, Dr. Hafiz Syaifullah Siregar, Dr. Giovani Christin Purba for assistance during data collection and data entry, typing, drafting, and writing the manuscript. We also thank Mr. Evan Susandi for his assistance in analyzing the data.

CONFLICT OF INTEREST

There are no conflicts of interest

REFERENCES

1. Xu P, Zhou Q, Xu J. Mechanism of thrombocytopenia in Covid-19 patients. Annals of Hematology. 2020;99:1205–1208
2. World Health Organization. WHO director general's remarks at the media briefing on 2019 nCov on 11 February 2020.
3. Huang C, Wang Y, Li X, Ren L, Zhao J, Zang Li, Fan G, *et al*. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. The Lancet. 2020;395: 497-506.
4. Liu J, Liu Y, Xiang P, Pu L, Xiong H, Li C, *et al.* Neutrophil-to lymphocyte ratio predicts severe illness patients with 2019 Novel Coronavirus in the Early Stage. MedRxiv. Available from https://doi.org/10.1101/2020.02.10.20021584
5. He F, Deng Y, Li W. Coronavirus Disease 2019 (COVID-19): What we know?. J Med Virol [Internet]. 2020 Mar 14; jmv.25766. Available

from: https://onlinelibrary.wiley.com/doi/abs/10.1002/jmv.25766

6. Adhikari SP, Meng S, Wu Y, Mao Y, Ye R, Wang Q, *et al*. Epidemiology, causes, clinical manifestation and diagnosis, prevention and control of coronavirus disease (COVID-19) during the early outbreak period: a scoping review. Infect Dis poverty [Internet]. 2020 Mar 17;9(1):29. Available from: http://www.preprints.org
7. WHO. Clinical management of severe acute respiratory infection when novel coronavirus (2019-nCov) infection is suspected. Interim guidance.
8. Y. Liu, X. Du, J. Chen, Y. Jin, L. Peng, H. Wang, *et al*. Neutrophil-to-lymphocyte ratio as an independent risk factor for mortality in hospitalized patients with COVID19, J Infect, 2020;81:e6-e12.
9. Naess A, Nilssen SS, Mo R, Eide GE, Sjursen H. Role of neutrophil to lymphocyte and monocyte to lymphocyte ratios in the diagnosis of bacterial infection in patients with fever. Infection [Internet]. 2017;45(3):299–307.
10. George Merekoulias, Evangelos C Alexopoulus, T. Belezos, E. Panagiotopoulou, E. Jelastopulu. Lymphocyte to monocyte ratio as a screening tool for influenza. PLoS Currents. 2010;2(MAR).
11. Mardani R, Ahmadi Vasmehjani A, Zali F, Gholami A, Mousavi Nasab SD, Kaghazian H, *et al*. Laboratory Parameters in Detection of COVID-19 Patients with Positive RT-PCR; a Diagnostic Accuracy Study. Arch Acad Emerg Med [Internet]. 2020;8(1):1-5.
12. Yang AP, Liu J, Tao W, Li H. The diagnostic and predictive role of NLR, d-NLR, and PLR in COVID-19 patients. International Immunopharmacology (2020). Available from:https://doi.org/10.1016/j.intimp.2020.106504
13. Song CY, Xu J, He JQ, Lu YQ. COVID-19 early warning score: a multi-parameter screening tool to identify highly suspected patients. medRxiv 8 March 2020. Available from: https://doi.org/10.1101/2020.03.05.20031906
14. Ish P, Malhotra N, Agrawal S, Gupta N. Relative lymphocytosis in COVID-19 -a ray of hope. Advances in Respiratory Medicine 2020;88(3):1–2.
15. Lin L, Lu L, Cao W, Li T. Hypothesis for potential pathogenesis of SARS-CoV-2 infection–a review of immune changes in patients with viral pneumonia. Emerging Microbes & Infections 2020;9:727-732.
16. Brzeszczyńska J. Quantitative Real-Time PCR application workshop. The University of the West of Scotland (UWS). Feb 2020. [Downloaded at 14 Agustus 2020]. Available from: https://www.breath-copd.org/app/uploads/2017/11/QPCR-training-Joanna-Brzeszczynska.pdf
17. Zheng S, Fan J, Yu F, Feng B, Lou B, Zou Q, *et al*. Viral load dynamics and disease severity in patients infected with SARS-CoV-2 in Zhejiang province, China, January-March 2020: retrospective cohort study. BMJ 2020;369:m1443
18. Warny M, Helby J, Nordestgaard BG, Birgens H, Bojesen SE. Lymphopenia and risk of infection and infection-related death in 98,344 individuals from a prospective Danish population-based study. PLOS Medicine, 1 November 2018. 1-22. Available from: https://doi.org/10.1371/journal.pmed.1002685
19. Xiang F, Zhu J, Cao X, Shen B, Zou J, Liu Z, *et al*. Lymphocyte depletion and subset alteration correlate to renal function in chronic kidney disease patients. Ren Fail, Early Online: 1–8. Available from: http://dx.doi.org/10.3109/0886022X.2015.1106871
20. Gu J, Korteweg C. Pathology and pathogenesis of severe acute respiratory syndrome. The American J Pathology, 2007;170:1136-1147.
21. Qin C, Zhou L, Hu Z, Zhang S, Yang S, Tao Y, *et al*. Dysregulation of immune response in patients with Coronavirus 2019 (COVID-19) in Wuhan, China. Clin Infect Dis. 2020;12:1–7.