15718-44854-1-PB.pdf

by

Submission date: 17-May-2023 01:44PM (UTC+0700)
Submission ID: 2095247332
File name: 15718-44854-1-PB.pdf (284.52K)
Word count: 5310
Character count: 27607

BERKALA KEDOKTERAN

doi: 10.20527/jbk.v19i1.15718

RESEARCH ARTICLE

OPEN ACCES

Relationship between C-Reactive Protein Levels, Lactate Dehydrogenase, and Neutrophil-to-Lymphocyte Ratio with Coronavirus Disease 2019 Severity

Hendra Wana Nur'amin[1*], I Nyoman Suarjana[2], Mohammad Rudiansyah[3], Nanang Miftah Fajari[4], Djallalluddin[5]

[1]Department of Pharmacology, Faculty of Medicine, Universitas Lambung Mangkurat, Banjarmasin, Indonesia

[2]Rheumatology Division, Department of Internal Medicine, Ulin General Hospital, Banjarmasin, Indonesia

[3]Nephrology and Hypertension Division, Department of Internal Medicine, Faculty of Medicine, Universitas Lambung Mangkurat, Banjarmasin, Indonesia

[4]Endocrine, Metabolic and Diabetes Division, Department of Internal Medicine, Ulin General Hospital, Banjarmasin, Indonesia

[5]Cardiology Division, Department of Internal Medicine, Faculty of Medicine, Universitas Lambung Mangkurat, Banjarmasin, Indonesia

Coresspondence Author: hendranuramin@ulm.ac.id

Abstract:

Risk stratification of Coronavirus disease 2019 (COVID-19) patients is very important to determine patient care and prognosis. The reliable parameters include C-reactive protein (CRP), lactate dehydrogenase (LDH), and neutrophil-lymphocyte ratio (NLR). This study aimed to determine the relationship between CRP, LDH, and NLR levels with the severity of COVID-19 patients. An observational study with a cross-sectional approach was conducted at Ulin Hospital Banjarmasin on 91 eligible subjects. A logistic regression test was conducted to determine the relationship between variables and the severity of COVID-19. The results showed that there was no significant relationship between CRP levels and the severity of COVID-19 (prevalence odds ratio (POR) 0.85, 95% confidence interval (CI 95%) 0.34-2.09, p=0.72). There was a significant difference between the mean LDH levels in severe COVID-19 compared to non-severe COVID-19 (1006 $\pm$ 601.77 vs 543.5 $\pm$ 480.41, p<0.001), with POR 4.23, 95% CI 95% 1.56-11.45, p=0.005; there was also a significant difference between the mean NLR values in severe COVID-19 compared to non-severe COVID-19 (9.01 $\pm$ 6.32 vs 5.38 $\pm$ 5.03, p=0.002) with POR of 12.21 CI 95% 3.80-39.31, p<0.001. This study showed that LDH levels and NLR values were important predictors of COVID-19 severity.

Keywords: COVID-19; CRP; LDH; NLR

Introduction

The coronavirus disease 2019 (COVID-19) is known to have started in December 2019 in China and has spread rapidly throughout the world.[1] Clinical symptom and laboratory test results categorize patients into severe cases of COVID-19 and non-severe cases of COVID-19. Patients with severe COVID-19 will have an increased intensive care unit (ICU) need and risk of death.[2]

Patients with confirmed COVID-19 mostly showed significant changes in the results of the complete blood count and inflammatory markers.[3] A combination of several laboratory tests can be used to demonstrate the inflammatory state and prognosis.[4] The C-reactive protein (CRP), lactate dehydrogenase (LDH), and neutrophil-lymphocyte ratio (NLR) are some of the indicators that are easily found and widely available in many health facilities.[5]

The previous meta-analysis found that the significant inflammatory parameters in COVID-19 cases were high CRP and LDH, leukopenia, and lymphopenia.[6] CRP, LDH, and NLR levels can affect the severity of COVID-19 patients and their prognosis. Identification of laboratory predictors for disease progression and severity is critical for patient risk stratification.[2,6] This study aimed to determine the relationship between CRP, LDH, and NLR levels with the severity of COVID-19 patients treated at Ulin Hospital Banjarmasin.

Methods

This study was an observational study with a cross-sectional approach to determine the relationship between CRP, LDH, and NLR levels with the severity of COVID-19 patients treated at Ulin Hospital Banjarmasin from 2020 to 2021. The population in this study was medical record data of patients diagnosed with COVID-19 with the RT-PCR swab method.

The inclusion criteria in this study were patients aged 18-65 years diagnosed with COVID-19 using the RT-PCR swab method who were treated at Ulin Hospital Banjarmasin. Exclusion criteria were patients with incomplete data and patients with cancer and immunodeficiency.

The independent variables in this study were levels of CRP, LDH, and NLR with the dependent variable being the severity of COVID-19 (severe and not severe). The confounder variables were age, gender, diabetes mellitus, hypertension, heart disease, chronic lung disease, cerebrovascular disease, chronic kidney disease, and smoking.

We categorized patients based on the following conditions: non-severe COVID-19 patients meet the following conditions: (1) Epidemiological history, (2) Fever or other respiratory symptoms, (3) Radiological abnormalities typical of viral pneumonia, and (4) Positive RT-PCR result for SARS-CoV-2; severe COVID-19 patients meet at least one of the following conditions: (1) shortness of breath, respiratory rate 30 breaths/min, (2) oxygen saturation (resting condition) 93%, (3) PaO2/FiO2 300 mmHg.[7] CRP levels were categorized as high if CRP levels $\geq$20.42 mg/dl and low CRP if CRP levels <20.42 mg/dl.[8] High LDH levels if LDH levels were $\geq$450 U/L and low LDH levels if LDH levels were <450 U/L.[9] The NLR value was high if the NLR value $\geq$3.13 and the NLR value was low if the NLR value <3.13.[10]

The data collected were tabulated. Descriptive data of patients were presented in tables and percentages which include data on patient characteristics. Bivariate analysis using logistic regression was conducted to determine the relationship between CRP, LDH, NLR, and the confounder variables.

This study obtained a certificate of ethical clearance from the faculty of medicine, Universitas Lambung Mangkurat with No. 116/KEPK-FK ULM/EC/IV/2022, certificate of research ethical clearance at Ulin hospital Banjarmasin No. 98/VIII-Reg-Riset/RSUDU/20, and research permit No.001/Kedokteran/Diklit/RSUDU/VIII/2020 to conduct research at Ulin Hospital Banjarmasin.

Results

Data from medical records were collected in the 2020-2021 period and 91 subjects were obtained. The baseline characteristics of subjects can be seen in table 1.

Table 1. Baseline characteristic

Subjects (n = 91)	Severe COVID-19 (n=62)		Non severe COVID-19 (n=29)	
Gender				
Man	47	(51.65%)	23	(25.27%)
Woman	15	(16.48%)	6	(6.59%)
Mean age (mean ± SD)	50.06	± 7.48 _	44.24	± 10.67
CRP level				
High (>20.42 mg/dl)	36	(39.56%)	18	(19.78%)
Low (<20.42 mg/dl)	26	(28.57%)	11	(12.09%)
Average (mean ± SD)	27.65	± 20.98	31.38	± 29.23
LDH level				
Height (>450 U/L)	52	(57.14%)	16	(17.58%)
Low (< 450 U/L)	10	(10.99%)	13	(14.29%)
Average (mean ± SD)	1014	± 601.77	543.5	± 480.41
NLR value				
Height ≥ 3.13	57	(62.64%)	14	(15.38%)
Low <3.13	5	(5.49%)	15	(16.48%)
Average (mean ± SD)	9.01	± 6.32	5.38	± 5.03
Comorbid				
Diabetes mellitus	15	(16.48%)	5	(5.49%)
Hypertension	19	(20.88%)	9	(9.89%)
Heart disease	3	(3.30%)	2	(2.20%)
Asthma	2	(2.20%)	0	(0%)
COPD	0	(0%)	0	(0%)
tuberculosis	2	(2.20%)	0	(0%)
Cerebrovascular disease	0	(0%)	0	(0%)
Chronic kidney disease	1	(1.10%)	0	(0%)
Smokers	14	(15.38%)	5	5.49%)

Bivariate analysis using logistic regression was conducted to determine the relationship between CRP, LDH, NLR, and the confounder variables. The logistic regression test in table 2 showed that there was no significant relationship between CRP levels and the severity of COVID-19 (*odds ratio* (OR) 0.85 95% confidence interval (CI) 0.34-2.09, p=0.72), there was a significant relationship between LDH levels and COVID-19 severity (OR 4.23, 95% CI 1.56-11.45, p=0.005) and a significant relationship between NLR and COVID-19 severity (OR 12.21 95% CI 3.80-39, 31, p<0.001).

Table 2. Analysis of the relationship between CRP levels and the severity of COVID-19

	p	OR	Upper limit	Lower limit
CRP level	0.72	0.85	0.34	2.09
LDH level	0.005	4.23	1.56	11.45
NLR value	<0.001	12.21	3.80	39.31

The relationship between other variables and the severity of COVID-19 can be observed in table 3. Parameters of gender, age, diabetes mellitus, hypertension, heart disease, chronic lung disease, cerebrovascular disease, chronic kidney disease, and smoking will be assessed to determine the magnitude of the relationship. to the severity of COVID-19.

Table 3. Analysis of the relationship between comorbid variables and the severity of COVID-19

Subjects (n = 91)	Logistic regression			
	p	OR	Upper limit	Lower limit
Gender				
Male	0.71	0.82	0.28	2.38
Female				
Comorbidities				
Diabetes mellitus	0.46	1.53	0.50	4.72
Hypertension	0.97	0.98	0.38	2.55
Heart disease	0.69	0.69	0.11	4.35
Smoke	0.56	1.30	0.45	4.35

The relationship between other variables and the severity of COVID-19 did not show a significant relationship, namely gender (OR 0.82, 95% CI 0.28-2.38, p=0.71), diabetes mellitus (OR 1.53, CI 95 % 0.50-4.72, p=0.46), hypertension (OR 0.98, 95% CI 0.38-2.55, p=0.97), heart disease (OR 0.69, CI 95% 0.11-4.35, p=0.69), and smoking (OR 1.30, 95% CI 0.45-4.35, p=0.56). Parameters of asthma, COPD, tuberculosis, cerebrovascular disease, and chronic kidney disease could not be analyzed by logistic regression because the cases in one or more groups were empty.

Discussion

A severe inflammatory response is associated with impaired immunity, resulting in an imbalanced immune response. Circulating inflammatory markers can represent inflammatory and immune states, so they can be potential predictors for risk stratification of COVID-19 patients.[7] The C-reactive protein (CRP), lactate dehydrogenase (LDH), and neutrophil-lymphocyte ratio (NLR) are some of the indicators that are easily found and widely available in many health facilities.[5]

CRP markers can be used as indicators of inflammation markers in the human body.[11] As an acute-phase protein, CRP increases dramatically within hours of infection and activates the complement system via the classical pathway and macrophages via the Fcγ receptor. CRP levels are elevated during inflammatory diseases and infections. C-reactive protein is created mainly in hepatocytes and several cells.[12] The CRP can act as a pro-inflammatory and anti-inflammatory molecule depending on which CRP isoform is released.[13] CRP levels can increase up to 1000-fold in bacterial infections and decrease suddenly as soon as the infection resolves.[12]

Many studies suggest the use of CRP as a prognostic biomarker in acute and chronic infections. Plasma CRP levels in COVID-19 cases rise to levels similar to those of a bacterial infection. Furthermore, CRP levels correlated with a worse prognosis in COVID-19 with an odds ratio of 18.9 and proved to be a reliable marker for various adverse processes, such as, for example, the need for mechanical ventilation.[11] High CRP levels predict the risk of intubation in stable COVID-19 hospitalized patients on admission.[14] A

mild increase in CRP may or may not be clinically significant, depending on the clinical condition of the patient. Clinical correlations must be taken into account when interpreting the results of the CRP test.[11]

This study showed no significant difference between the mean CRP levels in severe COVID-19 *vs* non-severe COVID-19 (table 2). The logistic regression test showed that CRP levels were not significantly associated with the severity of COVID-19 (OR 0.85 95% CI 0.34-2.09, p=0.72). The results of this study are different from the previous one where some reports show a difference in the average CRP levels in severe COVID-19 compared to non-severe COVID-19. This may be due to differences in study subjects, patient characteristics, comorbidities, and cut-off levels of CRP which have clinical implications for the severity of COVID-19.

Several studies report that CRP is an important indicator for the prognostic prediction of COVID-19 and a biomarker of mortality.[15] An understanding of the role of proinflammatory cytokines in the pathophysiology of COVID-19 is essential for the evaluation of anti-cytokine therapy. SARS-CoV-2 may be well adapted to humans and viral genomic RNA or intermediates cannot be recognized by the immune system for activation of the inflammatory cascade. Luo *et al.* (2020) reported that circulating levels of IL-2, IL-4, TNF-α, IFN-γ, and CRP was not associated with the severity of COVID-19 symptoms.[16]

COVID-19 has different features in terms of severity, mortality, and spread in different countries. Several variations in mortality rates have been observed in different countries.[17] Large differences in the haplotypes of human leukocyte antigens may evoke variability of immune responses to SARS-CoV-2, leading to variations in the disease severity. The causes of severity and death of COVID-19 require further investigation. Several reports suggest a cytokine storm correlates with the severity of COVID-19 patients. But correlation did not show causation. More viral replication may also drive the severity of COVID-19.[16]

Lactate dehydrogenase is a group of oxidoreductase isoenzymes that catalyze the reversible reaction between pyruvate and lactate.[18] LDH plays a very important role as a diagnostic biomarker for several common diseases such as cancer, thyroid disorders, tuberculosis, etc. LDH levels are associated with mortality in COVID-19. High serum LDH levels on admission were independently associated with in-hospital mortality.[19]

This study showed a significant difference between the mean LDH levels in severe COVID-19 *vs* non-severe COVID-19 (1006 $\pm$ 601.77 *vs* 543.5 $\pm$ 480.41, p<0.001). Logistic regression test showed that LDH levels increased the risk of COVID-19 severity >4-fold (OR 4.23, 95% CI 1.56-11.45, p=0.005). The results of this study were similar to previous studies where some reports show a difference in the mean levels of LDH in severe COVID-19 compared to non-severe COVID-19.

LDH is an intracellular enzyme found in cells in almost all organ systems, which catalyzes the interconversion of pyruvate and lactate, with the interconversion of NADH and NAD+ simultaneously.[9,18] Elevated LDH levels are associated with a 6-fold increase in the likelihood of severe COVID-19 illness. More importantly, an increase in LDH was associated with a >16-fold increase in the probability of death. Thus, the patient's LDH should be monitored closely for signs of disease progression or decompensation.[18]

Elevated LDH in patients with COVID-19 suggests lung and tissue injury. COVID-19 can cause inadequate tissue perfusion and multiple organ failure due to various mechanisms, including thrombosis, leading to elevated LDH. Thus, high LDH serves as a biomarker of disease severity.[20] Several studies reported that elevated LDH was independently associated with poor prognosis.[21]

Severe infection can cause cytokine-mediated tissue damage and LDH release. Because LDH is present in lung tissue (isozyme

3), patients with severe COVID-19 infection release greater amounts of LDH into the circulation which often progresses to acute respiratory distress syndrome. In addition, LDH levels are elevated in thrombotic microangiopathy, which is associated with renal failure and myocardial injury.[18,19]

LDH levels are associated with the development of COVID-19. One study found significantly higher LDH levels in ICU patients than in non-ICU. Because high LDH levels persisted in the number of days in ICU patients after admission, LDH may be a predictive marker for severe disease.[22] A multi-center study involving 1,099 patients reported supporting evidence linking levels of tissue damage and inflammation with elevated LDH levels.[23]

The neutrophil: lymphocyte ratio (NLR) is an indicator of systemic inflammation that plays a potential prognostic role in several clinical conditions including acute respiratory distress syndrome, liver disease, cardiovascular disease, and malignancy.[24] The NLR value appears to be more sensitive than the absolute neutrophil value or lymphocyte count in bacterial and viral pneumonia, which is a marker of the systemic inflammatory response.[25] The NLR at admission may be beneficial for initial risk stratification and prioritization of required resources.[24]

This study also showed a significant difference between the mean NLR values in severe COVID-19 *vs* non-severe COVID-19 (9.01 ± 6.32 *vs* 5.38 ± 5.03, p=0.002). Logistic regression test showed that NLR levels were associated with a risk of COVID-19 severity more than 12-fold (OR 12.21 95% CI 3.80-39.31, p<0.001). The results of this study are similar to previous studies where some reports indicate an association between NLR and COVID-19 severity.

NLR values are recognized to reflect a balance between innate and adaptive immune responses. NLR has previously been recognized as a diagnostic tool and predictive marker of disease severity in patients with influenza virus and other inflammatory diseases.[26] Several studies have also identified a role for NLR in distinguishing severe diseases and predicting mortality. NLR can predict death or ICU admission in COVID-19 patients.[27] Neutrophil survival appears to be extended for several days after viral infection. This prolonged activation in turn leads to the release of pro-inflammatory mediators and toxins, paving the way for the need for repeated measurements of NLR during hospitalization. Neutrophils may lead to nonspecific immunity that initiates the body's response to inflammation, while lymphocytes are protective elements against inflammation, which are important for an innate immune response during viral infection.[28]

Liu *et al.* showed that of the 245 hospitalized patients, there were 13.47.% severe COVID-19 patients. Multivariate analysis showed that there was an 8% higher risk of in-hospital death for each unit increase in NLR (OR = 1.08; 95% CI, 1.01 to 1.14; p = 0.0147). Compared with patients in the lowest tertile, the NLR of patients in the highest tertile had a >16-fold higher risk of death (OR = 16.04; 95% CI, 1.14-224.95; p = 0.0395) after adjustment analysis with potential confounder factors. The adjusted OR analysis for mortality was 1.10 in males for each unit increase in NLR (OR = 1.10; 95% CI, 1.02-1.19; p = 0.016).[29]

Kong *et al.* reported that of 210 COVID-19 patients, 37 were diagnosed with severe cases. The mean NLR in the severe group was higher than that in the non-severe group (6.6 *vs* 3.3, P < 0.001). The highest NLR tertile (5.1-19.7) showed a 5.9-fold increased incidence of severity (95% CI 1.3-28.5) compared to the lowest tertile (0.6-2.5) after adjustment for confounders. The number of T cells decreased significantly in the severe group (0.5 *vs* 0.9, P < 0.001). COVID-19 may primarily act on lymphocytes, particularly T lymphocytes. Patients with elevated NLR should be advised to stay in isolation with respiratory monitoring and supportive care.[30]

Yang *et al.* indicated that increasing NLR and age were significantly associated with

disease severity. The analysis showed that an increase in NLR (*hazard ratio* [HR] 2.46, 95% CI 1.98–4.57) and age (HR 2.52, 95% CI 1.65–4.83) as independent factors for poor clinical outcomes in COVID-19 patients.[7]

The patient's condition and the presence of comorbidities associated with the condition influence the prognosis and progression of COVID-19 disease. Patients with advanced age, diabetes mellitus, hypertension, low PaO2/FiO2 values, and delayed treatment are risk factors for severe and fatal diseases.[31] The current pandemic also brings a new situation related to cardiovascular complications and comorbidities that lead to hypertension and diabetes mellitus.[32]

Based on gender in this study, it was found that more men were treated (7 7%) with COVID-19 than women (23%), but there was no statistically significant relationship between gender and the severity of COVID-19 (OR 0, 82, 95% CI 0.28-2.38, p=0.71). Jin, *et al*. (2020) showed slightly different that men and women have the same prevalence. However, men with COVID-19 were more at risk for poorer outcomes and death, regardless of age.[33] Raimondi, *et al* (2021) showed that hospitalized women are less likely to die from COVID-19; however, once severe disease occurs, the risk of death is similar to that of men. These divergent results warrant further investigation regarding the role of gender in the clinical course and outcome of COVID-19.[34]

Some evidence suggests that multiple comorbidities are associated with the severity of COVID-19. Patients with diabetes mellitus, obesity, and hypertension with COVID-19 experience increased morbidity and mortality rates.[35] Mechanisms for increased severity and mortality among diabetic patients include changes caused by hyperglycemia in the immune system and increased inflammatory cytokines. The severe course and poorer outcome of SARS-Cov-2 infection in hypertensive patients are associated with a hyperinflammatory response and the development of a cytokine storm during the third phase of the disease. Cardiovascular disease has also been linked to increased COVID-19 mortality.[36]

Several studies have shown that hypertension and diabetes mellitus are the main comorbidities in COVID-19.[37] Diabetic patients with COVID-19 infection have a higher risk of being admitted to the ICU during infection and a higher risk of death. Hypertension is the most common cardiovascular comorbidity that appears to significantly increase the risk of death in COVID-19 patients. [38] In this study, analysis of the relationship between comorbidities and the severity of COVID-19 in this study did not find a significant relationship. This may be due to differences in study subjects and patient characteristics that have clinical implications for the severity of COVID-19.

We found several limitations in this study: (1) this study used a cross-sectional approach so that it only saw several limited data and conditions that occur at one point in time. Changes that may occur before and after taking were not carried out in this study, so they cannot explain a causal relationship; (2) the data were taken retrospectively using secondary medical record data and had a risk of recall bias. This limitation was solved by cross-matching between medical record data, other written reports, and laboratories; (3) differences in population conditions, comorbidities, examinations, and guidelines that cannot be controlled make the possibility for differences in disease outcomes so it must be very careful to generalize the data to other populations.

Conclusions

This study found that LDH and NLR levels were significantly associated with the severity of COVID-19, while CRP levels were not associated with the severity of COVID-19. Further study is recommended to determine several biomarkers to predict COVID-19 severity.

Acknowledgements

We would like to thank Ulin hospital Banjarmasin for this study.

Author Contribution

HWN worked on the study design and the manuscript. INS and MR were involved in planning and supervising the work. NMF and DJ performed the statistical analysis and interpreted the results. All authors agreed to the results and accepted the manuscript.

References

1. Oude Munnink BB, Worp N, Nieuwenhuijse DF, Sikkema RS, Haagmans B, Fouchier RAM, et al. The next phase of SARS-CoV-2 surveillance: real-time molecular epidemiology. *Nat Med.* 2021;27(September):29-34. doi:10.1038/s41591-021-01472-w
2. Sun P, Lu X, Xu C, Sun W, Pan B. Understanding of COVID-19 based on current evidence. *J Med Virol.* Published online 2020:0-1. doi:10.1002/jmv.25722
3. Jin Y-H, Cai L, Cheng Z-S, Cheng H, Deng T, Fan Y-P, et al. A rapid advice guideline for the diagnosis and treatment of 2019 novel coronavirus (2019-nCoV) infected pneumonia (standard version). *Mil Med Res.* 2020;7(1):4. doi:10.1186/s40779-020-0233-6
4. Okugawa Y, Toiyama Y, Yamamoto A, Shigemori T, Ide S, Kitajima T, et al. Lymphocyte-C-reactive Protein Ratio as Promising New Marker for Predicting Surgical and Oncological Outcomes in Colorectal Cancer. *Ann Surg.* 2020;272(2):342-351. doi:10.1097/SLA.0000000000003239
5. Ying H-Q, Deng Q-W, He B-S, Pan Y-Q, Wang F, Sun H-L, et al. The prognostic value of preoperative NLR, d-NLR, PLR, and LMR for predicting clinical outcomes in surgical colorectal cancer patients. *Med Oncol.* 2014;31(12):305. doi:10.1007/s12032-014-0305-0
6. Rodriguez-Morales AJ, Cardona-Ospina JA, Gutiérrez-Ocampo E, Villamizar-Peña R, Holguin-Rivera Y, Escalera-Antezana JP, et al. Clinical, laboratory and imaging features of COVID-19: A systematic review and meta-analysis. Travel *Med Infect Dis.* 2020;34(March):101623. doi:10.1016/j.tmaid.2020.101623
7. Yang A, Liu J, Tao W, Li H. The diagnostic and predictive role of NLR, d-NLR, and PLR in COVID-19 patients. *Int Immunopharmacol.* 2020;84(January):106504. doi:10.1016/j.intimp.2020.106504
8. Tan C, Huang Y, Shi F, Tan K, Ma Q, Chen Y, et al. C-reactive protein correlates with computed tomographic findings and predicts severe COVID-19 early. *J Med Virol.* 2020;92(7):856-862. doi:10.1002/jmv.25871
9. Poggiali E, Zaino D, Immovilli P, Rovero L, Losi G, Dacrema A, et al. Lactate dehydrogenase and C-reactive protein as predictors of respiratory failure in CoVID-19 patients. *Clin Chim Acta.* 2020;509(April):135-138. doi:10.1016/j.cca.2020.06.012
10. Liu J, Liu Y, Xiang P, Pu L, Xiong H, Li C, et al. Neutrophil-to-lymphocyte ratio predicts critical illness patients with 2019 coronavirus disease in the early stage. *J Transl Med.* 2020;18(1):1-12. doi:10.1186/s12967-020-02374-0
11. Esposito F, Matthes H, Schad F. Seven COVID-19 Patients Treated with C-Reactive Protein (CRP) *Apheresis*. Published online 2022.
12. Fazal M. C-Reactive Protein a Promising Biomarker of COVID-19 Severity. *Korean J Clin Lab Sci.* 2021;53(3):201-207. doi:10.15324/kjcls.2021.53.3.201
13. Sproston NR, Ashworth JJ. Role of C-Reactive Protein at Sites of Inflammation and Infection. Front Immunol. 2018;9. doi:10.3389/fimmu.2018.00754
14. Mueller AA, Tamura T, Crowley CP,

DeGrado JR, Haider H, Jezmir JL, et al. Inflammatory Biomarker Trends Predict Respiratory Decline in COVID-19 Patients. *Cell Reports Med.* 2020;1(8):100144. doi:10.1016/j.xcrm.2020.100144

15. Yan L, Zhang H-T, Goncalves J, Xiao Y, Wang M, Guo Y, et al. An interpretable mortality prediction model for COVID-19 patients. *Nat Mach Intell.* 2020;2(5):283-288. doi:10.1038/s42256-020-0180-7
16. Luo W, Zhang JW, Zhang W, Lin YL, Wang Q. Circulating levels of IL-2, IL-4, TNF-α, IFN-γ, and C-reactive protein are not associated with severity of COVID-19 symptoms. *J Med Virol.* 2021;93(1):89-91. doi:10.1002/jmv.26156
17. Chakrabarti SS, Kaur U, Banerjee A, Ganguly U, Banerjee T, Saha S, et al. COVID-19 in India: Are Biological and Environmental Factors Helping to Stem the Incidence and Severity? *Aging Dis.* 2020;11(3):480. doi:10.14336/AD.2020.0402
18. Henry BM, Aggarwal G, Wong J, Benoit S, Vikse J, Plebani M, et al. Lactate dehydrogenase levels predict coronavirus disease 2019 (COVID-19) severity and mortality: A pooled analysis. *Am J Emerg Med.* 2020;38(9):1722-1726. doi:10.1016/j.ajem.2020.05.073
19. Masumoto A, Kitai T, Matsumoto S, Kuroda S, Kohsaka S, Tachikawa R, et al. Impact of serum lactate dehydrogenase on the short-term prognosis of COVID-19 with pre-existing cardiovascular diseases. *J Cardiol.* 2022;79(4):501-508. doi:10.1016/j.jjcc.2021.12.014
20. Martha JW, Wibowo A, Pranata R. Prognostic value of elevated lactate dehydrogenase in patients with COVID-19: a systematic review and meta-analysis. *Postgrad Med J.* 2022;98(1160):422-427. doi:10.1136/postgrad med-2020-139542
21. Mikami T, Miyashita H, Yamada T, Harrington M, Steinberg D, Dunn A, et al. Risk Factors for Mortality in Patients with COVID-19 in New York City. *J Gen Intern Med.* 2021;36(1):17-26. doi:10.1007/s11606-020-05983-z
22. Ferrari D, Motta A, Strollo M, Banfi G, Locatelli M. Routine blood tests as a potential diagnostic tool for COVID-19. *Clin Chem Lab Med*. 2020;58(7):1095-1099. doi:10.1515/cclm-2020-0398
23. Guan W-J, Ni Z-Y, Hu Y, Liang W-H, Ou C-Q, He J-X, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. *N Engl J Med.* Published online 2020:1-13. doi:10.1056/NEJMoa2002032
24. Sarkar S, Khanna P, Singh AK. The Impact of Neutrophil-Lymphocyte Count Ratio in COVID-19: A Systematic Review and Meta-Analysis. *J Intensive Care Med.* 2022;37(7):857-869. doi:10.1177/08850666211045626
25. Huang Z, Fu Z, Huang W, Huang K. Prognostic value of the neutrophil-to-lymphocyte ratio in sepsis: A meta-analysis. *Am J Emerg Med.* 2020;38(3):641-647. doi:10.1016/j.ajem.2019.10.023
26. Liu S, Wang X, She F, Zhang W, Liu H, Zhao X. Effects of Neutrophil-to-Lymphocyte Ratio Combined With Interleukin-6 in Predicting 28-Day Mortality in Patients With Sepsis. *Front Immunol.* 2021;12. doi:10.3389/fimmu.2021.639735
27. Citu C, Gorun F, Motoc A, Sas I, Gorun OM, Burlea B, et al. The Predictive Role of NLR, d-NLR, MLR, and SIRI in COVID-19 Mortality. *Diagnostics.* 2022;12(1):2-11. doi:10.3390/diagnostics12010122
28. Xu Z, Shi L, Wang Y, Zhang J, Huang L, Zhang C, et al. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. *Lancet*

Respir Med. 2020;8(4):420-422. doi:10.1016/S2213-2600(20)30076-X

29. Liu Y, Du X, Chen J, Jin Y, Peng L, Wang HHX, et al. Neutrophil-to-lymphocyte ratio as an independent risk factor for mortality in hospitalized patients with COVID-19. *J Infect*. 2020;81:6-12. doi:10.1016/j.jinf.2020.04.002
30. Kong M, Zhang H, Cao X, Mao X, Lu Z. Higher level of Neutrophil-to-Lymphocyte is associated with severe COVID-19. *Epidemiol Infect*. Published online 2020:0-5. doi:10.1017/S0950268820001557
31. Han J, Shi L-X, Xie Y, Zhang Y-J, Huang S-P, Li J-G, et al. Analysis of factors affecting the prognosis of COVID-19 patients and viral shedding duration. *Epidemiol Infect.* 2020;148:e125. doi:10.1017/S0950268820001399
32. Tascioglu D, Yalta K, Yetkin E. Hypertension and diabetes mellitus in patients with COVID-19: a viewpoint on mortality. *Cardiovasc Endocrinol Metab.* 2020;9(3):108-109. doi:10.1097/XCE.0000000000000213
33. Jin J-M, Bai P, He W, Wu F, Liu X-F, Han D-M, et al. Gender Differences in Patients With COVID-19: Focus on Severity and Mortality. *Front Public Heal.* 2020;8. doi:10.3389/fpubh.2020.00152
34. Raimondi F, Novelli L, Ghirardi A, Russo FM, Pellegrini D, Biza R, et al. Covid-19, and gender: lower rate but same mortality of severe disease in women—an observational study. *BMC Pulm Med.* 2021;21(1):96. doi:10.1186/s12890-021-01455-0
35. Cummings MJ, Baldwin MR, Abrams D, Jacobson SD, Meyer BJ, Balough EM, et al. Epidemiology, clinical course, and outcomes of critically ill adults with COVID-19 in New York City: a prospective cohort study. *Lancet*. 2020;395(10239):1763-1770. doi:10.1016/S0140-6736(20)31189-2
36. Merga BT, Ayana GM, Raru TB, Alemu A, Negash B, Bekana M, et al. Association of Pre-Existing Comorbidities with Disease Severity Among COVID-19 Patients in Eastern Ethiopia. *Infect Drug Resist.* 2022;Volume 15:2825-2834. doi:10.2147/IDR.S362140
37. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet*. 2020;395(10223):497-506. doi:10.1016/S0140-6736(20)30183-5
38. Wardani EM, Nugroho RF, Bistara DN, Afiyah RK, Hasina SN, Septianingrum Y. Clinical Manifestations of COVID-19 Patients with Comorbid and Non-comorbid at Dr. Soetomo Hospital, Surabaya. *Open Access Maced J Med Sci.*2022;10(G):330-334. doi:10.3889/oamjms.2022.7582

15718-44854-1-PB.pdf

ORIGINALITY REPORT

12%	13%	20%	3%
SIMILARITY INDEX	INTERNET SOURCES	PUBLICATIONS	STUDENT PAPERS

PRIMARY SOURCES

1	oamjms.eu Internet Source	3%
2	mdpi-res.com Internet Source	3%
3	www.cambridge.org Internet Source	2%
4	Muntaha Fazal. "C-Reactive Protein a Promising Biomarker of COVID-19 Severity", The Korean Journal of Clinical Laboratory Science, 2021 Publication	2%
5	www.dovepress.com Internet Source	2%
6	www.worldwidejournals.com Internet Source	2%

Exclude quotes	On	Exclude matches	< 2%
Exclude bibliography	On		