HEMATOLOGIC PARAMETERS AS PREDICTOR OF COVID-19 SEVERITY

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ABSTRACT

Introduction: *To this day, COVID-19 still cause high mortality and morbidity in most cases. The severity of COVID-19 can be detected by simple tests such as complete blood counts which available in most health facilities. Through early detection of the estimated severity of COVID- 19, we may determine which patients need hospitalization or patients sufficient with self-isolation.* ***Methods:*** *We conduct an analytical, cross-sectional, retrospective study that analyzed the hematological parameters of 97 patients with positive rRT-PCR swabs in the period of March to August 2020. We compared hematologic parameters of COVID 19 patients with mild and moderate-severe. The receiver operating characteristic (ROC) curve, area under the curve (AUC), and Youden's index were created to determine the optimal cut-off value in predicting the degree of severity of COVID-19 patients.* ***Results:*** *Statistically significant differences (p <0.05) were found in the hematological parameters of neutrophils, NLR, PLR, MLR, ALC, lymphocyte, eosinophil, SGOT, SGPT, CRP, and calcium. SGPT parameter had the highest sensitivity value (94.4%), MLR had the highest specificity value (84.5%), and Hs-CRP had the highest AUC value (AUC 0.789).* ***Conclusion:*** *Certain hematological parameters may assist in early detection of the severity of a COVID-19 patient. Our findings may be useful to determine whether the patient requires hospitalization or self-isolation.*

Keywords: *COVID-19, Prognostic, Severity, Biomarkers, Hematologic Paramet*

ABSTRAK

Pendahuluan: Sampai saat ini COVID-19 masih menimbulkan mortalitas dan morbiditas yang tinggi. Tingkat keparahan COVID-19 dapat dideteksi dengan pemeriksaan sederhana seperti darah lengkap yang tersedia di hampir semua

fasilitas kesehatan. Melalui deteksi dini perkiraan tingkat keparahan COVID-19, maka kita dapat memutuskan pasien yang membutuhkan rawat inap dan pasien yang cukup dengan isolasi mandiri. **Metode:** Penelitian analitik, cross-sectional, retrospektif yang menganalisa parameter hematologis pada 97 pasien dengan hasil swab rRT-PCR positif pada periode Maret hingga Agustus 2020. Parameter hematologis dibandingkan pada pasien COVID-19 dengan derajat keparahan ringan dan sedang-berat. Kurva *receiver operating characteristic* (ROC), area under the curve (AUC), dan *Youden's index* dibuat untuk menentukan nilai cut-off optimal dalam memprediksi derajat keparahan pasien COVID-19. **Hasil:** Perbedaan bermakna ($p < 0,05$) didapati pada parameter hematologis neutrofil, NLR, PLR, MLR, ALC, limfosit, eosinofil, SGOT, SGPT, CRP, dan calcium. Parameter SGPT memiliki nilai sensitivitas tertinggi (94,4%), MLR memiliki nilai spesifitas yang paling tinggi (84,5%), dan Hs- *CRP memiliki nilai AUC paling tinggi (AUC 0,789).* ***Kesimpulan:*** *Parameter hematologis tertentu dapat digunakan sebagai deteksi dini derajat* keparahan pasien COVID-19. Hal tersebut sangat penting dalam menentukan apakah pasien tersebut memerlukan rawat inap atau dapat isolasi manndiri.

Kata Kunci : COVID-19, Prognosis, Derajat Keparahan, Parameter Hematologis, Biomarker

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INTRODUCTION

In December 2019, an outbreak of acute respiratory infection occurs in the city of Wuhan, Hubei, China which identified as Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2).[1] The World Health Organization (WHO) publicize a new name for the disease called Coronavirus Disease 2019 (COVID-19). In March 2020 WHO announced COVID-19 as a pandemic.[2] In Indonesia, more than 600,000 cases were reported and more than 18,000 deaths and this number is still growing.

Based on the Clinical management of COVID-19 from

WHO, the severity of COVID-19 is classified into mild, moderate, severe, and critical. Mild disease include fever (83-99%), cough (59-82%), fatigue(44-70%), anorexia (40-84%), shortness of breath (31-40%), myalgia (11 -35%), and non-specific symptoms such as sore throat, nasal congestion, headache, diarrhea, nausea and vomiting. *Anosmia* and *ageusia* are reported to precede the onset of respiratory symptoms. Moderate disease were clinical symptoms of pneumonia, but no signs of severe pneumonia, including SpO2 ≥ 90% on room air. Severe disease are clinical signs of pneumonia accompanied by one or more symptoms of the following: respiratory rate>30 breaths/minute; severe respiratory distress; or SpO2 <90% on room air.[3]

The critical disease refers to ARDS (acute respiratory distress syndrome) symptoms with an onset of less than 1 week in patients with pneumonia or new cases or worsening of respiratory symptoms. Bilateral opacities, collapsed lungs or nodules were found on radiological images of the lungs or CT scan or ultrasound of the lungs. ARDS itself is divided into mild, moderate, and severe. Mild ARDS was marked as 200 mmHg <PaO2 / FiO2 a ≤ 300 mmHg (with PEEP or CPAP ≥ 5 cmH2O); moderate ARDS was marked as 100 mmHg <PaO2 / FiO2 ≤ 200 mmHg (with PEEP ≥ 5 cmH2O); and severe ARDS characterized by PaO2 / FiO2 ≤ 100 mmHg (with PEEP ≥ 5 cmH2O). Critical disease can also be found in patients with sepsis, septic shock, and multiple organ failure.[3]

A study by Wang et al in China found hematological value could be utilized as parameter of severity in COVID-19, specifically the NLR value.[4] Asghar et al confirmed a significant increase in NLR and PLR values in patients with severe COVID- 19 infection.[5] Other studies have explained that hematological parameters such as leucocyte value (WBC), leucocyte count (differential count), liver function (SGOT / SGPT), CRP are one of the tools to predict the prognosis of COVID-19.[6] Elshazli et al emphasized hematological parameters are a reliable tool in predicting the morbidity rate of COVID-19 infection so that periodic measurements are needed to monitor

the severity of the disease[7].

Nganjuk Regional General Hospital (RSUD) is one of the COVID-19 referral hospitals in East Java, specifically in Nganjuk Regency. The incidence of COVID-19 infection in Nganjuk as of July has reached 90 confirmed COVID-19, 70 cases of suspected COVID-19 and 100 cases of probable COVID-19. Based on these data, this study aims to determine the role of hematological values in predicting the severity of COVID-19.

METHOD

This research is an analytical, observational, and retrospective study at Nganjuk hospital. Samples in this study were all COVID-19 patients at Nganjuk Hospital who were diagnosed using rRT-PCR from March 2020 to September 2020, totaling 97 patients. A total of 58 of them were mild cases and 39 patients had COVID 19 moderate-severe cases. Classifications were divided using the WHO classification. Data from patients and laboratory values were taken from medical record data.

Data analysis was using the IBM SPSS version 23. The normality of data distribution was determined using the Kolmogorov Smirnov test. Parametric data were displayed in numbers and percentages. Parametric data with abnormal distribution were displayed using median and Q1-Q3. Odd ratios were used in presenting risk factors data for patients to fall in a condition of severe severity. We used Chi-square test to analyze categorical variables, independent T-test to analyze parametric variables that were normally distributed, and the Mann-Whitney U to analyze parametric variables with abnormal distribution. Parametric variables that were statistically significant were analyzed with the receiver operating characteristic (ROC) curve, area under the curve (AUC), and Youden's index (J) were used to determine the optimal cut-off value in predicting the severity of COVID-19. In this study, 95% confidence interval (CI) was used and p value <0.05 was considered statistically significant

RESULTS

Table 1. showed the clinical characteristic of patients with COVID-19 infection with a total sample of 97 in which divided into two groups: moderate-severe group (n = 39) and mild group (n = 58). In the

moderate-severe group, the average age of the patients was 46 years with mostly male (64.1%). Whereas in the mild severity group, the majority were female (56.9%) with an average age of patients who were younger (40.5 years) than the moderate-severe group. Fever were the most prevalent complaints in the moderate-severe group (79.5%) and mild group (55.2%). There are statistically significant differences between two groups on the parameters of age, gender, clinical symptoms of cough, and clinical symptoms of dyspnea ($p < 0.05$). Subjects in the moderate-severe group had clinical symptoms of fever, cough and dyspnea which were more common than those in the mild group.

Table 1. Clinical Characteristic COVID-19 Patients

Clinical characteristic		Covid-19 degree of severity		OR	P value
		Moderate-Severe (n = 39)	Mild (n = 58)		
Age (years)		46 (38 – 60)	40,5 (23,75 – 48)		0,002*
Gender	Male	25 (64,1%)	25 (43,1%)	2,357	0,042*
	Female	14 (35,9%)	33 (56,9%)		
Fever	Yes	31 (79,5%)	32 (55,2%)	3,14	0,014*
	No	8 (20,5%)	26 (44,8%)		
Cough	Yes	29 (74,4%)	28 (48,3%)	3,11	0,011*
	No	10 (25,6%)	30 (51,7%)		
Dyspnea	Yes	22 (56,4%)	16 (27,6%)	3,397	0,004*
	No	17 (43,6%)	42 (72,4%)		
Mialgia	Yes	2 (5,1%)	2 (3,4%)	1,80	0,683
	No	37 (94,9%)	56 (96,6%)		
Gastrointestinal disturbance	Yes	7 (17,9%)	7 (12,1%)	1,59	0,419
	No	32 (82,1%)	51 (87,9%)		

Table 1. showed the laboratory description of COVID-19 patients. In this study, results of significant comparisons were found in neutrophils, lymphocytes, eosinophils, NLR, ALC, PLR, MLR, SGOT, SGPT, BUN, creatinine, calcium, and Hs-CRP. Neutrophil, NLR, PLR, MLR, SGOT, SGPT, BUN, Sc, and CRP values were higher in the moderate-severe severity group than in mild severity group. Lymphocyte, ALC, and calcium values were found to be lower in the moderate-severe degree group than in the mild-grade group.

Table 2. Laboratory Characteristic of COVID-19

Laborator Parameter	Covid-19 Degree of Severity				P value
	Mild	Q1-Q3	Moderate-Severe	Q1-Q3	
Hb (g/dl)	13,8 (n = 58)	12,7 – 15,05	13,6 (n = 39)	12,7 – 15,4	0,941
Leukocyte	9.400 (n = 58)	7.145 -11.637,5	8.960 (n = 39)	6.730 – 12.620	0,607
Neutrophil (%)	63,95 (n = 58)	56,57 – 70,72	73,9 (n = 39)	70,5 - 82,4	0,000*
Lymphocyte (%)	25,15 (n = 58)	20,75 – 33,47	17,4 (n = 39)	9,5 – 22,9	0,000*
Monocyte (%)	6,75 (n = 58)	5,62 – 8,65	6,9 (n = 39)	5,2 – 8,9	0,777
Eosinophil (%)	1,25 (n = 58)	0,55 – 2,25	0,25 (n = 39)	0 – 1,1	0,000*
Basophil (%)	0,4 (n = 58)	0,2 – 0,7	0,35 (n = 39)	0,17 – 0,7	0,766
Hematocrit	40,9 (n = 58)	37,45 – 44,62	41,6 (n = 39)	37,3 – 43,5	0,912
MCV	82,8 (n = 58)	79,4 – 86,82	82,3 (n = 39)	78,1 – 85,8	0,373
Trombocyte	278.500 (n = 58)	245.250 – 340.500	233.000 (n = 39)	173.000 – 413.000	0,167
MPV	9 (n = 58)	6,94 – 10,225	7,3750 (n = 39)	6,6 – 10,02	0,317
NLR	2,5075 (n = 58)	1,7 – 3,48	4,2356 (n = 39)	3,07 – 9,29	0,000*
ALC	2.129,81 (n = 58)	1.555,88 – 3.148,31	1.230,88 (n = 39)	968,5 – 1.898,88	0,000*
PLR	120,6831 (n = 58)	90,50 – 168,57	170,997 (n = 39)	108,69 – 253,55	0,012*
MLR	0,2817 (n = 58)	0,20 – 0,37	0,4619 (n = 39)	0,267 – 0,704	0,001*
SGOT	24,6 (n = 48)	18,8 – 40,8	47,1 (n = 36)	29,225 – 76,825	0,000*
SGPT	27,1 (n = 48)	16,95 – 44,15	46,9 (n = 36)	32,525 – 67,1	0,001*
De Ritis Rasio	0,93 (n = 48)	0,75 – 1,45	1,006 (n = 36)	0,65 – 1,50	0,849
BUN	9 (n = 40)	7 – 12,75	13 (n = 34)	10 – 16	0,002*
Creatinine	0,81 (n = 40)	0,72 – 0,99	0,96 (n = 35)	0,81 – 1,2	0,009*
Sodium	136 (n = 36)	132 – 138,75	134 (n = 29)	129 – 137	0,107
Potassium	3,7 (n = 35)	3,4 – 4,0	3,7 (n = 29)	3,4 – 3,9	0,828
Calcium	1,17 (n = 35)	1,12 – 1,23	1,12 (n = 29)	1,04 – 1,16	0,004*
Hs-CRP	1,845 (n = 24)	0,21 – 7,44	20,135 (n = 18)	4,7 – 89,03	0,001*

* = Significant mann Whitney-U test ($p < 0,05$)

Hb: Hemoglobin; MCV: Mean cell volume; MLR: Monocyte lymphocyte ratio; NLR: Neutrophils lymphocyte ratio; PLR: Platelet lymphocyte ratio; SGOT: Serum Glutamic Oxaloacetic Transaminase; SGPT: Serum Glutamic Pyruvic Transaminase; MPV: Mean platelet volume; ALC: Absolute lymphocyte count; Hs-CRP: High-sensitivityC-reactive protein; Na: Natrium; K: Kalium; Ca: Calcium

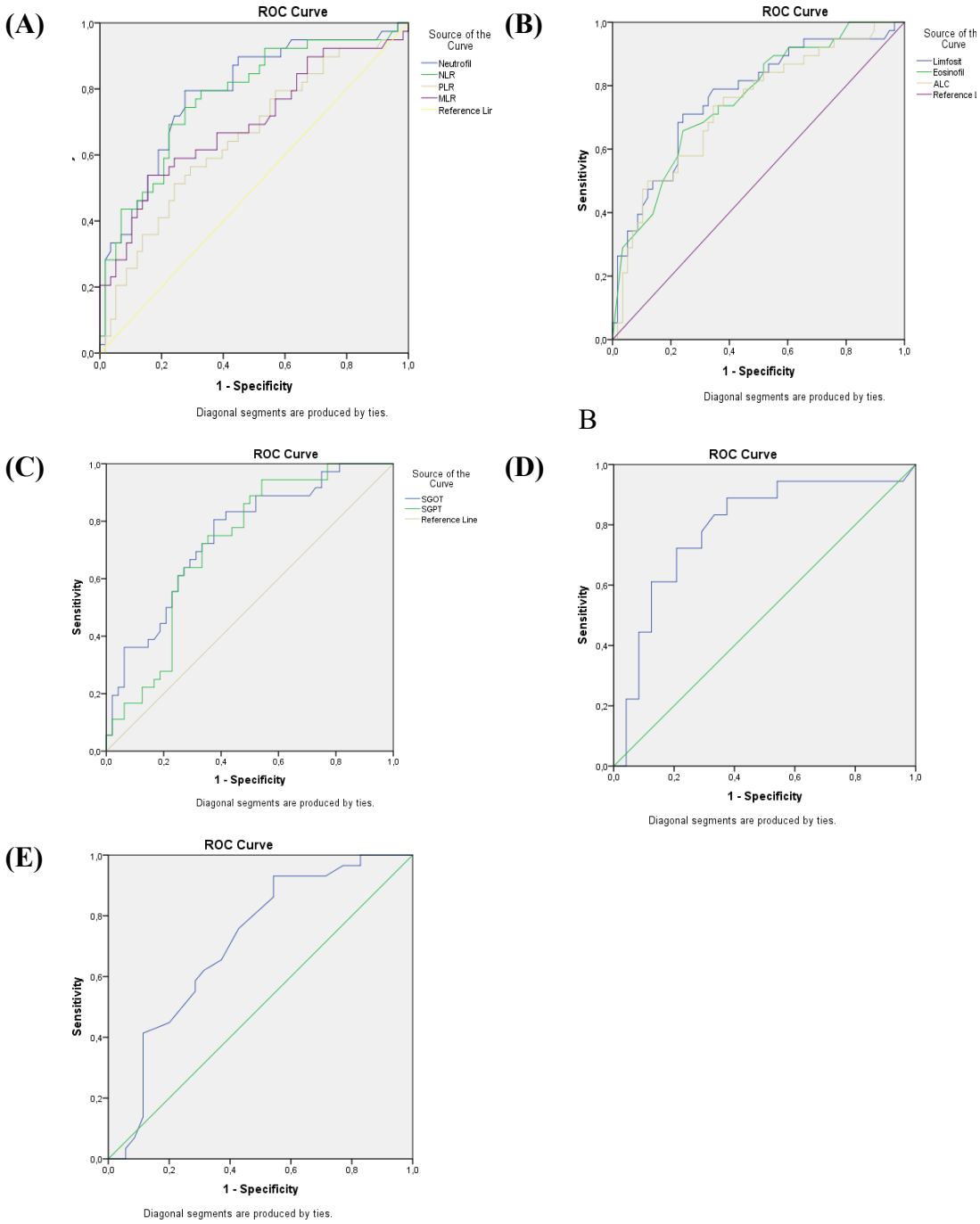

Figure 1. Receiver Operating Characteristic (ROC) curve was performed to evaluate the cut off value of the hematological parameters in determining degree of severity of COVID-19. **(A)** The diagnostic value of neutrophils, NLR, PLR, MLR in determining the degree of severity in patients with COVID-19. **(B)** Diagnostic value of lymphocytes, eosinophils, and ALC in determining the degree of severity in patients with COVID-19. **(C)** The diagnostic value of SGOT and SGPT in determining the degree of severity in patients with COVID-19.**(D)** The diagnostic value of Hs-CRP in determining the degree of severity in patients with COVID-19. (E) The diagnostic value of Calcium in determining the degree of severity in patients with COVID-19**.**

All parameters (neutrophils, NLR, PLR, MLR, lymphocytes, eosinophils, ALC, SGOT, SGPT, Hs-CRP, and Ca) were analyzed by ROC and have a statistically significant p value ($p < 0.05$). SGPT parameters (cut off ≥ 23.3; AUC 0.717; CI 0.608-0.826) had the highest sensitivity value (94.4%) in predicting the occurrence of moderate-severe degrees of severity in patients with COVID-19. Meanwhile, MLR parameter (cut off ≥ 0.4351; AUC 0.695; CI 0.583-0.806) had the highest specificity value (84.5%) in predicting the occurrence of moderate-severe severity in patients with COVID-19. The highest AUC value was found in the Hs-CRP parameter (cut off ≥ 3.08; AUC 0.789; CI 0.643-0.936) with a sensitivity of 88.9% and a specificity of 62.5%. (Table 3)

Table 3. Cut Off Value

Parameter	Cut off	Sensitivity	Spesificity	AUC	CI 95%	P value
Neutrophil (%)	≥ 70,05	79,5%	72,4%	0,787	0,693-0,881	,000*
NLR	≥ 3,547	69,2%	77,6%	0,776	0,680-0,872	,000*
PLR	≥ 169,1386	51,3%	75,9%	0,651	0,538-0,763	,012*
MLR	≥ 0,4351	53,8%	84,5%	0,695	0,583-0,806	,001*
Lymphocyte (%)	≤ 20,8	71,1%	75,9%	0,766	0,667- 0,865	0,000*
Eosinophil (%)	≤ 0,5	65,8%	75,9%	0,756	0,659- 0,853	0,000*
ALC	≤ 1837,875	73,7%	65,5%	0,735	0,632- 0,838	0,000*
SGOT	≥ 28,10	80,6%	62,5%	0,745	0,640-0,850	0,000*
SGPT	≥ 23,30	94,4%	45,8%	0,717	0,608-0,826	0,001*
Hs-CRP	≥ 3,08	88,9%	62,5%	0,789	0,643-0,936	0,001*
Ca	≤ 1,185	93,1%	45,7%	0,711	0,584-0,839	0,002*

MLR: Monocyte lymphocyte ratio; NLR: Neutrophils lymphocyte ratio; PLR: Platelet lymphocyte ratio; SGOT: Serum Glutamic Oxaloacetic Transaminase; SGPT: Serum Glutamic Pyruvic Transaminase; ALC: Absolute lymphocyte count; Hs-CRP: High-sensitivity C-reactive protein; Ca: Calcium

DISCUSSION

Mortality and morbidity rates of COVID-19 patients are still relatively high and puts a lot of burden in the community. From a complete blood count, we may obtain inflammatory markers such as NLR, MLR, PLR, and ALC which might be able to predict the severity of COVID-19 patients.

This study found male have risk factors for falling in a more

severe condition than female. This study is in line with previous studies that found the severity and mortality of men was higher than women.[8] This result is likely due to higher estrogen levels in women. Estrogen has an anti- inflammatory effect that inhibits the inflammatory response.[9] This study found older people are more likely to have a higher degree of severity. Other studies found old age may be a predominant risk factor for severity and morbidity in COVID-19 patient.[8] The number of neutrophil counts in the mild group were lower than moderate- severe group. This result is in accordance with several previous meta-analysis studies which found higher neutrophil count value was commonly found in the severe and critical groups of COVID-19 patients and could be used as a predictor of the severity of COVID-19.[10,11]

Eosinophil count value in the mild group was significantly higher than that in the moderate-severe group (1,250 vs 0.250). A study in China stated that patients with COVID-19 which treated in isolation rooms were more likely to be transferred to the ICU compared to groups with normal eosinophil values.[12] A study by Liu F. in China stated during the treatment period, the number of eosinophil counts increased earlier in mild COVID-19 cases than in moderate-severe cases. Increasing in number of eosinophils during the treatment period is also in line with the improvement in radiological and virological laboratory.[13]

This study found lymphocyte count in the mild group was significantly higher than in moderate-severe group. Lymphopenia is the most common hemotological abnormalities in COVID-19 patients, which is around 35-85%.[14–16] Jiang et al. evaluated the lymphocyte counts in 103 patients and found that CD3 +, CD4 +, and CD8 + cells and NK cells decreased significantly in COVID-19 patients, specifically in severe and critical COVID-19 patients.[17]

NLR, PLR, and MLR are biomarkers that are widely studied in COVID-19 patients. MLR, PLR, and MLR indicate the inflammatory status of patient and are also biomarkers that could predict the prognosis of COVID-19 patients.[18,19]

High NLR, PLR, and MLR were predictors of the occurrence of severe COVID-19.[18,20,21] Previous studies also obtained similar results. NLR, PLR, and MLR were higher in COVID-19 patients who were admitted to the ICU. Lymphocytes are the target of the virus because the SARS- CoV-2 virus bind to the angiotensin converting enzyme 2 (ACE-2) receptor found on lymphocytes.[22,23] Our study found high NLR, PLR and MLR values could be used as predictors of severe COVID-19.

Our study found low ALC value is a predictor of severe COVID-19. Another study in United States found lower ALC in patients admitted to the ICU compared to non-ICUs patients. This finding is supported by a study in Singapore in which lower ALC values were found in ICU patients.[24] Research in India showed significantly lower ALC values in symptomatic COVID-19 patients compared to asymptomatic patients.[25]

COVID-19 infection causes damage to various organs including liver. This happens because coronavirus binds to ACE-2 receptors in hepatocytes and cholangiocytes.[26] Based on a meta-analysis study, there was an increase in liver enzymes with an increase in SGOT by 21% and SGPT by 30% in patients with mild symptoms and an increase in SGOT by 48% and SGPT 38% in severe cases.[27] A significant increase in SGOT was found in Wuhan in 62% of ICU patients and 25% in non-ICU patients.[28] Our study found SGOT and SGPT were predicting factors with a high sensitivity of 80.6% and 94.4%, respectively.

Our study found an increasing CRP value in the moderate-severe group compared to the mild-severity group. CRP has a high sensitivity, namely 88.9% with a cutoff of ≥ 3.08. Increased value of CRP are a predictor for severity in patients with COVID-19.[29] Increased level of CRP correlates with lung lesions and the severity of the disease. [30,31]

Our study found BUN and serum creatinine were significantly higher in the moderate-severe group. The interaction of the SARS-CoV-2 virus and the ACE-2 receptor in the kidneys caused abnormal activation of the renin-angiotensin-aldosterone system (RAAS) which increased

water absorption in the renal tubules and increased urea reabsorption, which will increase BUN levels in the blood.[32] This has been proven in 6.7% of patients with SARS infection experiencing acute kidney failure (AKI), and 37% in COVID-19 patients.[32,33]

The results showed calcium has a sensitivity of 93.1% with a cutoff of ≤ 1.185. Our study showed a decrease in calcium levels in the moderate-severe group compared to the mild group. In vitro experiments and animal models shown SARS-CoV-E gene encodes a small transmembrane protein with ion channel activity that is synthesized during infection and suggest that changes in calcium homeostasis within cells can increase the activation of the inflammatory pathway leading to increased levels of IL-1b, TNF, and IL-6, associated with pulmonary cell damage[34]

LIMITATIONS

Limitations in this study are the relatively small number of patients. Hematological parameter data taken are not dynamically followed until patients are discharged. Patients' comorbid disease was not further evaluated .For further studies, it is recommended to investigate the development in the patients' hematological parameters.

CONCLUSION

The hematological parameters in COVID-19 may help us predict the severity of COVID 19 and determine the appropriate treatment for the patients. Numbers of COVID-19 patients which relatively increased every day, makes it necessary for us to sort out patients who need hospitalization or self-isolation. Complete blood as a simple test may help us predict the severity of COVID-19 patients. Through this research, it is hoped by examining certain hematological parameters, we may determine the degree of severity of COVID-19 patients.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest in this study

AUTHOR CONTRIBUTION

All authors were participating actively in research and article writing and partly responsible for the content of this writing, including in the preparation and writing of concepts, designs, analysis, or

revision of the article.

RESEARCH ETHICS

This research was conducted in accordance with the research regulations set by the "World Medical Association Helsinki Declaration". This study has also received approval from the ethics committee of the Nganjuk Regional General Hospital, Indonesia**.**

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