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ORIGINAL RESEARCH

Neutrophil-to-Lymphocyte Ratio and Cut-off Values as Predictor of Severity and Mortality in COVID-19 Patients in Millennium COVID-19 Care Center, Addis Ababa, Ethiopia

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Background: Early identification of patients at high risk of poor clinical outcomes is the key to success in saving the lives of patients with coronavirus disease 2019 (COVID-19). Neutrophil to Lymphocyte Ratio (NLR) is an easily available and cheap surrogate inflammatory marker, its baseline NLR role in African COVID-19 patients remains to be investigated. The objective of the study aimed to evaluate the role of NLR as a predictor of severity and mortality of COVID-19 patients admitted at the Millennium COVID 19 care center in Addis Ababa, Ethiopia.

Methods: A cross-sectional study was conducted on patients with COVID-19 admitted to the Millennium COVID-19 care center from August 1 to October 30, 2021. Receiver Operating Characteristic curve analysis was used to calculate the area under the curve to assess the predictive capacity of NLR on mortality and severity. Multivariable logistic regression analysis was done to identify the association between independent variables and disease outcomes with an Adjusted Odds Ratio (AOR), P-value, and 95% CI for AOR were used for testing significance.

Results: The NLR of 9.47 was identified as the optimal cut-off value for predicting mortality with a sensitivity of 88.7% and a specificity of 95.4% (Area Under the Curve (AUC):0.95, 95% CI 0.92–98; P<0.001) and the NLR of 5.86 was an effective threshold value in predicting the severity of disease with a sensitivity of 92.2% and a specificity of 75% (AUC:0.85, 95% CI 0.800–0.905; P<0.001). In multivariable logistic regression analysis, after adjusting for confounding factors, NLR of more than 9.47 and 5.86 was significantly associated with all-cause of in-hospital mortality (AOR=4.73, 95% CI, 1.19–33.68; P<0.02), and severity of disease (AOR=12.98, 95% CI 3.85–43.80; P=0.001), respectively.

Conclusion: NLR greater than 9.47 and 5.86 effectively predict mortality and severity of the disease, respectively. It provides an objective input for early decision-making in inpatient management especially in resources limited area.

Keywords: COVID 19, neutrophil-to-lymphocyte ratio

Introduction

Coronavirus disease 2019 (COVID-19), a highly infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has spread fast over the world and continues to pose a significant danger to global public health and has resulted in huge stress on the health care systems of all countries in the world, especially resource-limited areas.[1,2]

According to the WHO COVID 19 dashboard, as of March 21, 2022, there were over 470 million confirmed cases worldwide, with a death toll of over 6 million. In Africa, more than 8.5 million individuals have been infected, with

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a death toll of over 170,000. Regarding the Ethiopian context, there were 469 thousand confirmed cases and 7489 patients died.[3]

After virus entry into the cell, the intracellular antiviral mechanisms lead to the secretion of interferons (IFNs), which trigger an inflammatory response characterized by an initial cytokine storm (hyper-inflammation) that results in acute respiratory distress syndrome (ARDS), followed by immune deregulation that causes sepsis-related fatalities such as septic shock.[4–6]

The majority of COVID-19 patients develop mild (40%) or moderate (40%) illness, with approximately 15% developing severe disease requiring oxygen assistance and 5% developing critical conditions with complications. Several factors have been identified as risk factors for disease severity and mortality including comorbidities (ie diabetes, hypertension, obesity, chronic lung disease, cancer, and cardiovascular diseases), age >65, current smoking, ethnicity, and genetic predisposition.[6–8]

In terms of laboratory tests, the main characteristics of COVID-19 are normal or decreased a total number of white blood cells count, decreased lymphocyte count, increased IL-6, CRP, ESR, procalcitonin, liver enzymes, D-dimer, lupus anticoagulant, von Willebrand factor, ferritin, and lactate dehydrogenase are implicated as indicators of disease severity, progression, and outcome.[6,9–12]

Some of these laboratory markers (D-dimer, ferritin, lactate dehydrogenase, procalcitonin, IL-6) are often expensive and time-consuming, jeopardizing the patient's treatment. Hence, investigating simple, reliable, and accurate biomarkers is mandatory for the early identification of patients who are at high risk of poor clinical outcomes is a key to success in the management of the disease and saving the lives of patients with coronavirus disease 2019 (COVID-19), especially in developing countries like Ethiopia where there is a significant shortage of ICU setup, limited resources and limited manpower.[6,9–11,13,14]

Neutrophil to lymphocyte ratio (NLR), which is cheap and easily computed from a routine blood test by dividing the absolute neutrophil count by the absolute lymphocyte count, has great value in indicating a patient's overall systemic inflammatory status. Its changes can not only reflect the role of neutrophils in infection but also reflect the changes of lymphocytes. According to recent studies, NLR has some predictive value in the diagnosis and predicting the severity and mortality in patients with COVID-19, which could potentially aid in risk stratification models for predicting severe and fatal outcomes.[9,10,15]

However, its use in the clinical setting has been overlooked due to the lack of a well-established optimal cutoff point at the specific treatment center or locality, and its significance in predicting mortality and severity among COVID 19 patients in our country and across Africa remains unknown.

So far, research on COVID-19 in Ethiopia and Africa at large has mainly focused on the epidemiology, treatment outcome, clinical features, time of recovery and gross laboratory biomarkers that predict mortality and morbidity.[16–18]

To our knowledge, no study has been conducted with a particular focus on NLR in Africa setup as an independent predictor of severity and mortality of COVID-19. Therefore, the study aimed to evaluate the predictive value of NLR on the severity and mortality of COVID-19 patients admitted to the millennium COVID-19 care center in Addis Ababa, Ethiopia.

Methods and Materials

Study Design and Setting

A retrospective cross-sectional study was conducted on patients diagnosed with COVID-19 and admitted to the Millennium COVID-19 Care Center (MCCC), a makeshift hospital in Addis Ababa, located near Bole airport. It is designed to accommodate 1040 patients, of which 40 are intensive care unit beds.

Population and Sampling Frame

The source population was all individuals with a confirmed COVID 19 were admitted to the Millennium COVID-19 Care Center (MCCC) from August 1 to October 30/2021 and all COVID 19 patients who fulfilled the inclusion criteria were selected as study participants and the lists of admitted COVID 19 patients at MCCC during the study period were taken as a sampling frame.

Inclusion Criteria and Exclusion Criteria

All adult (age > 18 years old) patients who were diagnosed with COVID-19 and had a complete blood count on the first day of admission were included in the study. The Exclusion Criteria were: (1) Patients with an incomplete chart, like missing clinical and hematology data, and those without clinical outcomes data were excluded from the study. (2)

Patients who were referred from other centers after several days of hospitalization without an attached admission complete blood count (CBC) in the first center. (3) Those with solid malignancy on chemotherapy and hematological disorders like myeloma, leukemia and lymphoma, and patients with documented glucocorticoids exposure before admission were excluded from the study.

Sample Size and Sampling Procedure

The sample size was determined by using a single population proportion formula, with the assumption of a 20% proportion (P) of severe COVID 19 in regional and local area reports,[19] 95% confidence level (1.96), 5% desired precision (d) and 5% non-response rate was considered due the assumption of study participants (survivors) and family member of selected non survivors were refused the consent via phone call. The final sample size was 240 (n) COVID-19 patients. A systematic random sampling technique was employed to select the study participants. To select the first participant, a simple random sampling technique (lottery method) was used, and then every Kth interval was followed until the pre-determined sample size (240) was obtained.

Study Variables

The study variables were selected after reviewing relevant literature according to the objective of the research and by considering the local context of the study area. The dependent variables were in-hospital mortality and severity of COVID-19.

The independent variables were socio-demographic characteristics, clinical factors, laboratory findings (neutrophil to lymphocyte ratio), and interventions.

Operational Definitions

COVID-19 severity score was determined based on the WHO classification as follows.[6]

Mild Disease: patients with symptoms of COVID-19 include fever, cough, lethargy, upper respiratory symptoms, and/or less common symptoms (headache, loss of taste or smell, etc.)

Moderate Disease: Patients with lower respiratory symptom/s. They may have infiltrates on the chest X-ray. These patients can maintain oxygenation saturation on atmospheric air.

Severe Disease: These patients have developed complications. Severe sickness can be defined by the following characteristics.

- Hypoxia: $SPO_2 < 93\%$ on ambient air or $PaO2:FiO_2 < 300mmHg$.
- Tachypnea: respiratory discomfort or RR more than 30 breaths per minute.
- Chest x-ray: More than 50% involvement was found on chest imaging.

Critical COVID 19: As defined by the criteria for acute respiratory distress syndrome (ARDS), sepsis and septic shock that require the provision of life-saving therapies such as mechanical ventilation (invasive or non-invasive) or vasopressor therapy.

Data Collection and Quality Assurance

Data was collected by well-trained residents and general practitioners by using a semi-structured pretested questionnaire developed from a standard WHO COVID 19 questionnaire and different literature. Data were checked for completeness, accuracy, clarity, and consistency by supervisors before data entry, and data cross-checking was done before analysis.

Data Analysis

IBM SPSS Statistics version 26 software was used for the statistical analysis. The categorical variables were described as numbers and percentages and analyzed by cross-tabulation and χ^2 test. Receiver operating characteristic (ROC) curve analysis was used to assess the predictive capacity of NLR on mortality and Severity and to state the optimal cutoff value, sensitivity, and specificity of NLR for all-cause mortality and disease severity. These results were reported as area

under the curve (AUC) and 95% confidence intervals (CI). Then we regrouped the patients based on the NLR cutoff value for each severity and mortality. The odds ratios were calculated by comparing the occurrence of death or severe disease in two different groups of independent variables. In addition, to adjust for potential confounding with variables, bivariable and multivariable logistic regression models were used.

Bivariable logistic regression analysis was done to screen out independent variables at a 25% level of significance, and those significant variables were incorporated into the analysis of multivariable logistic regression. For multivariable logistic regression, a 95% confidence interval for an Adjusted Odds Ratio (AOR) was calculated, and variables with a p-value ≤ 0.05 were considered statistically associated with disease outcome and severity.

Ethical Consideration

Ethical clearance and approval were obtained from the Institutional Review Board (IRB) of St. Paul Hospital Millennium Medical College (Ref No. pm 23/324). Supporting letter of permission was obtained from MCCC medical head office. Informed verbal consent was obtained from survivors study participants and non-survivor patient's next of kin via phone call. Medical registration numbers were used for data collection, and no personal identifiers were collected or used in the research report. Access to the collected information was limited to data collectors and the principal investigator, and confidentiality was maintained throughout the study. All methods were performed in accordance with the relevant guidelines and regulations and were in compliance with the Declaration of Helsinki.

Results

Socio-Demographics, Comorbidity, and Presenting Symptoms

A total of 240 COVID-19 patients with complete medical records were included in the current study. Among the 240 patients, 138 (57.5%) of the study subjects were males, and the mean age of the patients was 54 (±15.3) years. The most common symptoms at presentation were cough (59.2%) and shortness of breath (26.3%). Regarding the baseline comorbidity information, 145 (60.4%) had a preexisting one or more co-morbid illnesses and the most prevalent comorbidities were hypertension 95 (39.6%) and diabetes mellitus 83 (34.6%) (Table 1).

Baseline Laboratory Finding

The initial laboratory indicators of patients are presented in Table 2. Most 136 (56.7%) patients having normal white blood cell count with 40 (16.7%) patients had leukopenia and 64 (26.7%) having leukocytosis. The median absolute neutrophil count was $6.05\times 10^3/\mu L$ (IQR: 4.55–10.12) and median absolute lymphocyte counts was $0.95\times 10^3/\mu L$ (IQR: 0.65–1.35). More than half (53.7%) of patients had lymphopenia and majority 198 (82.5%) of patients had normal platelet count with thrombocytopenia and thrombocytosis identified in 33 (13.8%) and 9(3.8%) of cases, respectively. More than two-thirds (78.2%) of patients having raised urea and 24 (11.9%) had raised creatinine. Concerning liver enzymes, deranged levels of Serum Glutamic Oxaloacetic Transaminase (SGOT), Glutamic Pyruvic Transaminase (SGPT), and Alkaline Phosphatase (ALP) were identified on 95 (40.6%), 66 (28.4%), and 37 (15.9%) of the patients, respectively (Table 2).

Severity and Disease Outcome of COVID-19

Among the 240 patients studied, almost half the patients 116 (48.3%) had severe disease (38.8% severe and 9.6% critical) and the rest 124 (51.6%) had non-severe diseases (27.9% mild and 23.8% moderate) at admission. Regarding disease outcome, a quarter (25.85%) of patients died.

Receiver Operating Characteristic (ROC) Curve Analysis

The ROC curves were analyzed and were plotted for NLR for mortality and severity of COVID 19 (Table 3).

The analysis of the ROC curve illustrated a 0.95 area under the curve (AUC) for NLR levels as a predictor of in-hospital mortality (95% CI: 0.92–0.98, $P < 0.0001$). The AUC of this biomarker indicated a high predictive value for the outcome, with the optimal threshold value being 9.47 with a sensitivity of 88.7% and a specificity of 95.0%. The corresponding positive and negative predictive values were 62.5% and 95.4%, respectively (Figure 1).

Table 1 Socio-Demographic, Co-Morbid Illness and Presenting Chief Compliant Among COVID-19 Patients Admitted at MCCC, Addis Ababa, Ethiopia, 2021

Variables		Frequency (%)
Age	<30	27(11.3)
	30–49	63(26.3)
	50–69	93(38.8)
	>70	57(23.8)
Gender	Male	138(57.5)
	Female	102(42.5)
Chief compliant	Cough	142(59.2)
	Shortness of breath	63(26.3)
	Fever	14(5.8)
	Fatigability, loss of appetite, loss of test and smell	16(6.7)
	Other (Headache, Arthralgia and myalgia)	6(2.5)
Comorbidity	NO	95(39.6)
	YES	145(60.4)
Hypertension	NO	145(60.4)
	YES	95(39.6)
Diabetes mellitus	NO	157(65.4)
	YES	83(34.6)
CKD	NO	226(94.2)
	YES	14(5.8)
HIV/AIDS	NO	233(97.0)
	YES	7(2.9)
Cardiac disease	NO	219(91.3)
	YES	21(8.8)
Malignancy	NO	234(97.5)
	YES	6(2.5)
COPD and Asthma	NO	223(92.9)
	Yes	17(7.1)
Other	NO	228(95)
	YES	12(5)

Note: Data are expressed as n (%).
Abbreviations: CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; HIV, human immunodeficiency virus; MCCC, millennium covid-19 care center.

Regarding the ROC curve for the severity of COVID 19, a NLR of 5.86 was demonstrated as the optimal cut-off value as a predictor of severe disease with a sensitivity of 92.2% and a specificity of 75% (area under the curve (AUC): 0.858, 95% CI 0.80–0.90; P= 0.0001) (Figure 2).

Table 2 Baseline Laboratory Findings on the Admission of COVID 19 Patients Admitted at MCCC, Addis Ababa, Ethiopia, 2021

Variables		Frequency (%)
White blood cell	<4.5 x10^3 /μ l	40(16.7)
	4.5–11 x10^3 /μ l	136(56.7)
	>11 x10^3 /μ l	64(26.7)
Platelet	<150 x10^3 /μ l	33(13.8)
	150–450 x10^3 /μ l	198(82.5)
	>450 x10^3 /μ l	9(3.8)
Hemoglobin	<12 mg/dl	37(15.4)
	12–15 mg/dl	119(49.6)
	>15 mg/dl	84(35.0)
Hematocrit	<36%	44(18.3)
	36–45%	128(53.3)
	>45%	68(28.3)
Urea	<20mg/dl	52(21.8)
	>20mg/dl	187(78.2)
Creatinine	<0.6mg/dl	62(30.8)
	0.6–1.1mg/dl	115(57.2)
	>1.2mg/dl	24(11.9)
ALT/GPT	<40 IU/l	166(71.6)
	>40 IU/l	66(28.4)
AST/GOT	<40 IU/l	139(59.4)
	>40 IU/l	95(40.6)
ALP	<130 IU/l	196(84.1)
	>130 IU/l	37(15.9)
Total Bilirubin	<0.2 mg/dl	19(15.3)
	0.2–1.2 mg/dl	95(76.6)
	>1.2 mg/dl	10(8.1)

Note: Data are expressed as n (%).
Abbreviations: ALP, alkaline phosphatase; GOT, glutamic oxaloacetic transaminase; GPT, glutamic pyruvic transaminase; MCCC, millennium covid-19 care center.

Clinical Factors and Laboratory Biomarkers Related Variables and Comparison Between Non-Severe with Severe and Survivor with Non-Survivor Groups in COVID-19 Patients

A higher proportion of COVID-19 disease severity was observed among the groups classified by Age 50–69, age >70, presence of shortness of breath, presence of comorbidity, and presence of HTN, DM and cardiac disease (Table 4).

Table 3 ROC Value for Inflammatory Markers for Predicting COVID 19 Mortality and Severity

Variables	AUC	Cutoff	Sensitivity	Specificity	PPV	NPV
NLR for severity	0.85	5.86	92.2%	75%	77.5%	91%
NLR for mortality	0.95	9.47	88.7%	95.4%	62.5%	95.4%

Abbreviations: AOR, adjusted odds ratio; AUC, area under the curve; NLR, neutrophil to lymphocyte ratio; NPV, negative predictive value; PPV, positive predictive value; ROC, receiver operating characteristic curve.

Among the vital sign and laboratory markers; high respiratory rate, low oxygen saturation, leucocytosis, thrombocytosis, raised ANC, lymphopenia, elevated BUN, and deranged both GOT and GPT were observed in a large proportion of severe groups (Table 5).

Predictors of COVID 19 Mortality

In bivariable logistic regression, a 25% level of significance (P<0.25) was conducted and some factors were found significantly associated with the outcome (in-hospital death). These factors were: Age greater than 65, sex, presence of comorbidity, presence of Hypertension, presence of diabetes, presence of CKD, and presence of HIV/AIDS.

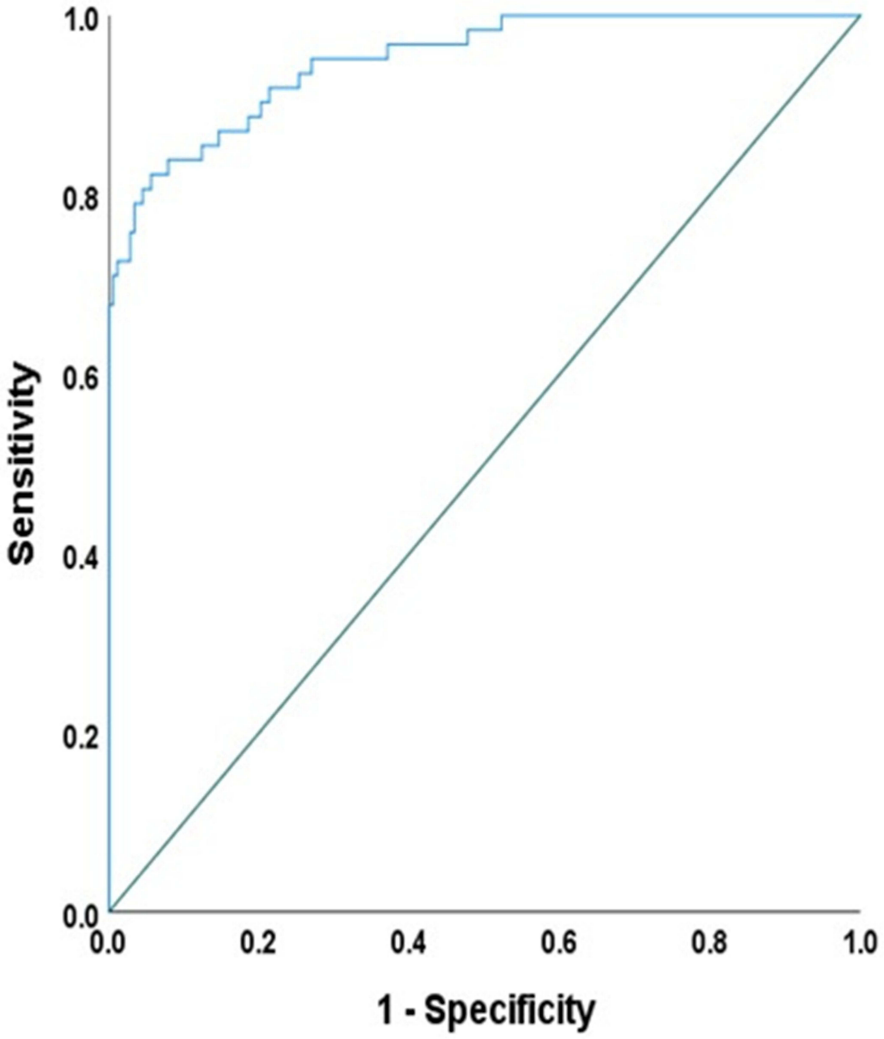

Figure 1 ROC curves of neutrophil to lymphocyte ratios in predicting mortality of COVID-19 patients.

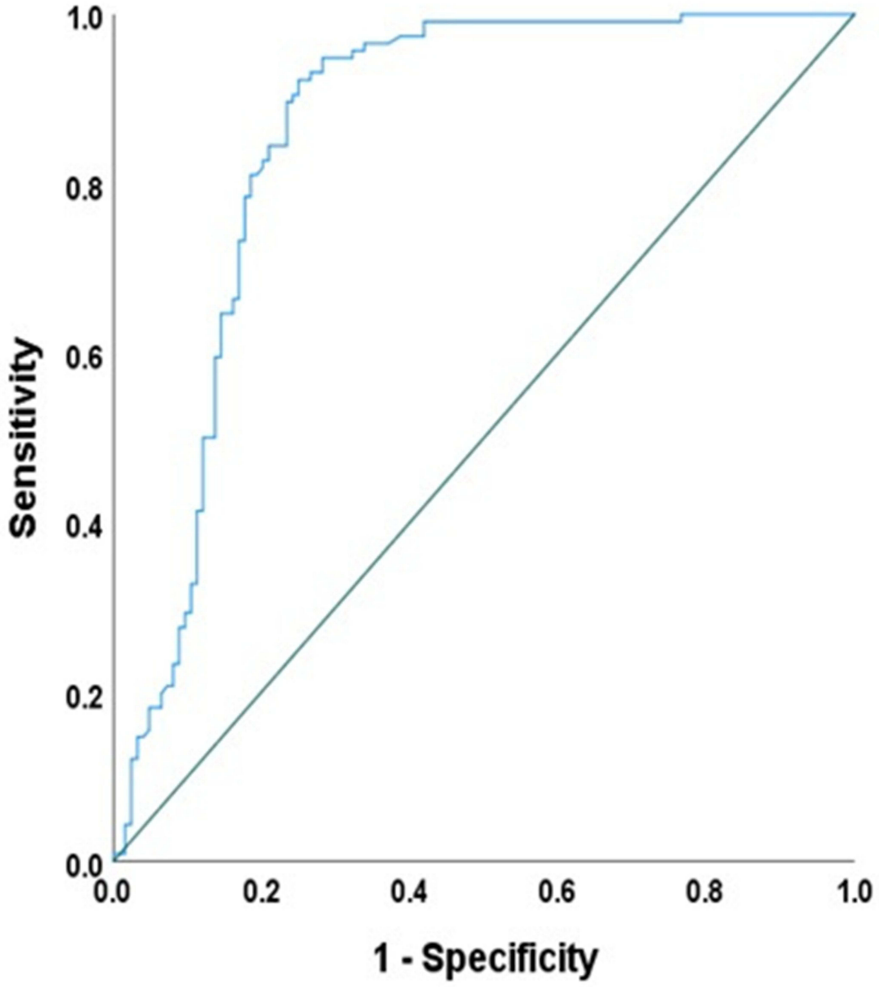

Figure 2 ROC curves of neutrophil to lymphocyte ratios in predicting severity of COVID-19 patients.

Among vital signs and laboratory markers that affect in-hospital death, the following factors were; respiratory rate above 20, systolic and diastolic hypertension, low hemoglobin concentration, high WBC count, high absolute neutrophil count, low absolute lymphocyte count, raised creatinine, high aspartate aminotransferase, and high NLR had significant association on crude analysis at 25% of significance.

However, based on the multivariable logistic regression model at a 5% level of significance, leukocytosis, lymphopenia, anemia and NLR of > 9.47 were found significant association with the disease outcome (Table 6).

Predictors of COVID-19 Severity

A crude analysis of each independent variable with severity of disease was run at a 25% level of significance ($P < 0.25$), several factors: age greater than 65, presence of diabetes, hypertension, malignancy, a respiratory rate greater than 20, elevated blood pressure, increase in WBC, increase in NLR, increased absolute neutrophil count, low absolute lymphocyte count, raised urea, and deranged liver enzymes (GOT and GPT) were found to be significantly associated with COVID-19 disease outcome.

However, only high NLR (> 5.86), a decrement in absolute lymphocyte count, and an elevated level of GOT/AST were found to be significantly associated with disease severity in the multivariable binary logistic regression model at a 5% level of significance (Table 7).

Table 4 Comparison of Socio Demography and Comorbid Illness Variables Between Non-Severe with Severe and Survivor with Non-Survivor Groups in COVID-19 Patients at MCCC, Addis Ababa, Ethiopia, 2021

Variables		Outcome		Severity	
		Survivor n (%)	Death n (%)	Non-Severe n (%)	Severe n (%)
Age group	<30	25(92.6)	2(7.4)	22(81.5)	5(18.5)
	30–49	52(82.5)	11(17.5)	38(60.3)	25(39.7)
	50–69	65(69.9)	28(30.1)	42(45.2)	51(54.8)
	>70	36(63.2)	21(36.8)	22(38.6)	35(61.4)
Gender	Male	107(77.5)	31(22.5)	70(50.7)	68(49.3)
	Female	71(69.6)	31(30.4)	54(52.9)	48(47.1)
Chief Complaint	Cough	110(77.5)	32(22.5)	75(52.8)	67(47.2)
	Shortness of breath	41(65.1)	22(34.9)	19(30.2)	44(69.8)
	Fever	12(85.7)	2(14.3)	13(92.9)	1(7.1)
	Fatigability, loss of test and smell	12(75)	4(25)	12(75)	4(25)
	Headache, arthralgia and myalgia	3(60%)	2(40%)	5(100%)	0(0%)
Comorbidity	NO	84(88.4)	11(11.6)	55(57.9)	40(52.1)
	YES	94(64.8)	51(35.2)	69(47.6)	76(52.4)
Hypertension	NO	122(84.1)	23(15.9)	86(59.3)	59(40.7)
	YES	56(58.9)	39(41.1)	38(40)	57(60)
Diabetes mellitus	NO	127(80.9)	30(19.1)	89(56.7)	68(43.3)
	YES	51(61.4)	32(38.6)	35(42.2)	48(57.8)
Chronic kidney disease	NO	170(75.2)	56(24.8)	113(50)	113(50)
	YES	8(57.1)	6(42.9)	11(78.6)	3(21.4)
HIV/AIDS	NO	174(75.7)	56(25.3)	120(51.5)	113(48.5)
	YES	4(40.0)	3(42.9)	4(57.4)	3(42.9)
Cardiac Disease	NO	163(74.4)	56(25.6)	114(52.1)	105(47.9)
	YES	15(71.4)	6(28.6)	10(47.6)	11(52.4)
Malignancy	NO	174(74.4)	60(25.6)	119(50.9)	115(49.1)
	YES	4(66.7)	2(33.3)	5(83.3)	1(16.7)
COPD and Asthma	NO	166(74.4)	57(25.6)	115(51.6)	108(48.4)
	Yes	12(70.6)	5(29.4)	9(52.9)	8(47.1)

Note: Data are expressed as n (%).
Abbreviations: COPD, chronic obstructive pulmonary disease; HIV, human immunodeficiency virus; MCCC, millennium covid-19 care center.

Regarding on the impact of NLR on serious clinical complication and subsequent need of ICU admission and usage of invasive ventilation, we further divided patients into two groups using NLR greater than or less than 5.86 as the criterion to compared, therefore those patients who had NLR of greater than 5.86 were significantly higher rate of admission to the ICU (80.4% vs 13.7%) and usage of invasive ventilation (41.3% vs 2.9%), and development of serious clinical complication (48.6% vs 3.9%) as compared with those with NLR <5.86 ($p<0.001$) (Table 8).

Table 5 Laboratory Biomarker, Vital Sign Related Variables and Comparison Between Non-Severe with Severe and Survivor with Non Survivors of COVID-19 Patients Among Patients Admitted at MCCC, Addis Ababa, Ethiopia, 2021

Variables		Outcome		Severity	
		Survivor n (%)	Death n (%)	Non-Severe n (%)	Severe n (%)
SBP	<140mmHg	137(76.1)	43(23.9)	100(55.6)	80(44.4)
	≥140mmHg	41(68.3)	19(31.7)	24(40)	36(60)
DBP	<90mmHg	168(76.4)	52(23.6)	118(53.6)	102(46.4)
	≥90mmHg	10(50)	10(50)	6(30)	14(70)
Temperature	≤37.5°C	167(73.9)	59(26.1)	113(50)	113(50)
	>37.5°C	11(78.6)	3(21.4)	11(78.6)	3(21.4)
RR	<30breath/min	152(77.9)	43(22.1)	117(60)	78(40)
	≥30breath/min	26(57.8)	19(42.2)	7(15.6)	38(84.4)
PR	≥100beat/min	116(74.8)	39(25.2)	84(54.2)	71(45.8)
	>100breat/min	62(72.9)	23(27.1)	40(47.1)	45(52.9)
SO_2	>93%	81(65.3)	43(34.7)	9(7.3)	115(92.7)
	≤93%	97(83.6)	19(16.4)	0(0%)	116(99.1)
White blood cell	<4.5 x10^3/μL	36(90)	4(10)	33(82.5)	7(17.5)
	4.5–11x10^3/μL	114(83.8)	22(16.2)	77(56.6)	59(43.4)
	>11 x10^3/μL	28(43.8)	36(56.3)	14(21.9)	50(78.1)
Platelet	<150 x10^3/μL	22(66.7)	11(33.3)	20(60.6)	13(39.4)
	150–450 x10^3/μL	150(75.8)	48(24.2)	101(51.0)	97(49.0)
	>450 x10^3/μL	6(66.7)	3(33.3)	3(33.3)	6(66.7)
Hemoglobin	<12 mg/dl	18(48.6)	19(51.4)	25(67.6)	12(32.4)
	12–15 mg/dl	87(73.1)	32(26.9)	56(47.1)	63(52.9)
	>15 mg/dl	73(86.9)	11(13.1)	43(51.2)	41(48.8)
Hematocrit	<36%	23(52.3)	21(47.7)	28(63.6)	16(36.4)
	36–45%	102(79.7)	26(20.3)	64(50)	64(50)
	>45%	53(77.9)	15(22.1)	32(47.1)	36(52.9)
ANC	<6.5 x10^3/μL	115(93.5)	8(6.5)	91(74)	32(26)
	>6.5 x10^3/μL	63(53.8)	54(46.2)	33(28.2)	84(71.8)
ALC	>1.1 x10^3/μL	107(96.4)	4(3.6)	87(78.4)	24(21.6)
	<1.1 x10^3/μL	71(55)	58(45)	37(28.7)	92(71.3)
Urea	<20 mg/dl	45(86.5)	7(13.5)	37(71.2)	15(28.8)
	>20mg/dl	133(71.1)	54(28.9)	87(46.5)	100(53.5)

(*Continued*)

Table 5 (Continued).

Variables		Outcome		Severity	
		Survivor n (%)	Death n (%)	Non-Severe n (%)	Severe n (%)
Creatinine	<0.6 mg/dl	47(75.8)	15(24.2)	36(58.1)	26(41.9)
	0.6–1.1mg/dl	91(79.1)	24(20.9)	57(49.6)	58(50.4)
	>1.2mg/dl	12(50)	12(50)	13(54.2)	11(45.8)
ALT/GPT	<40 IU/l	125(75.3)	41(24.7)	94(56.6)	72(43.4)
	>40 IU/l	48(72.7)	18(27.3)	26(39.4)	40(60.6)
AST/GOT	<40 IU/l	108(77.7)	31(22.3)	86(61.9)	53(38.1)
	>40 IU/l	67(70.5)	28(29.5)	36(37.9)	59(62.1)
ALP	<130 IU/l	152(77.6)	44(22.4)	104(53.1)	92(46.9)
	>130 IU/l	22(59.5)	15(40.5)	18(48.6)	19(51.4)
Total Bilirubin	<0.2mg/dl	18(94.7)	1(5.3)	10(52.6)	9(47.4)
	0.2–1.2mg/dl	68(71.6)	27(28.4)	47(49.5)	48(50.5)
	>1.2mg/dl	9(90)	1(10)	5(50)	5(5)

Note: Data are expressed as n (%).
Abbreviations: ALC, absolute lymphocyte count; ALP, alkaline phosphatase; ANC, absolute neutrophil count; DBP, diastolic blood pressure; GPT, glutamic oxaloacetic transaminase; GPT, glutamic pyruvic transaminase; PR, pulse rate; RR, respiratory rate; SBP, systolic blood pressure; SO_2, oxygen saturation.

Discussion

In the current study, we conducted a retrospective cross-sectional study to evaluate the predictive potential of NLR as a predictor of mortality and severity of disease among 240 COVID 19 patients who were admitted to the Millennium

Table 6 Bivariable and Multivariable Analysis for Risk Factors Associated with Mortality Patients with COVID-19 (n=240)

Variables		Outcome		COR(95% CI)	AOR(95% CI)	P-value
		Survivor n (%)	Death n (%)			
Age	<65	138(78.9)	37(21.1)	1	1	
	≥65	40(61.5)	25(38.5)	2.33(1.25–4.32)	1.27(0.41–3.95)	0.668
Gender	Male	107(77.5)	31(22.5)	1	1	
	Female	71(69.6)	31(30.4)	1.50(0.84–2.69)	1.67(0.60–4.67)	0.322
Comorbidity	NO	84(88.4)	11(11.6)	1	1	
	YES	94(64.8)	51(35.2)	4.14(2.02–8.46)	0.71(0.11–4.53)	0.721
Hypertension	NO	122(84.1)	23(15.9)	1	1	
	YES	56(58.9)	39(41.1)	3.69(2.02–6.76)	3.26(0.84–12.70)	0.088
DM	NO	127(80.9)	30(19.1)	1	1	
	YES	51(61.4)	32(38.6)	2.65(1.46–4.81)	1.85(0.48–7.07)	0.365

(*Continued*)

Table 6 (Continued).

Variables		Outcome		COR(95% CI)	AOR(95% CI)	P-value
		Survivor n (%)	Death n (%)			
CKD	NO	170(75.2)	56(24.8)	1	1	
	YES	8(57.1)	6(42.9)	2.27(0.75–6.84)	0.23(0.02–4.23)	0.328
HIV/AIDS	NO	174(75.7)	56(25.3)	1	1	
	YES	4(40.0)	3(42.9)	4.66(1.27–17.11)	17.58(0.81–381.19)	0.068
SBP	<140mmHg	137(76.1)	43(23.9)	1	1	
	>140mmHg	41(68.3)	19(31.7)	1.47(0.77–2.80)	1.54(0.48–4.92)	0.459
DBP	<90mmHg	168(76.4)	52(23.6)	1	1	
	>90mmHg	10(50)	10(50)	3.23(1.27–8.18)	1.43(0.27–7.44)	0.671
RR	<20breath/min	49(80.3)	12(19.7)	1	1	
	>20breath/min	129(72.1)	50(27.9)	1.58(0.77–3.22)	0.61(0.16–2.22)	0.456
WBC	<4.5, 4.5–11	150(85.2)	26(14.8)	1		
	>11 $x10^3/\mu L$	28(43.8)	36(56.3)	7.41(3.89–14.15)	3.60(1.01–12.79)	0.047*
ANC	<6.5 $x10^3/\mu L$	115(93.5)	8(6.5)	1	1	
	≥6.5 $x10^3/\mu L$	63(53.8)	54(46.2)	12.32(5.51–27.52)	3.84(0.84–17.54)	0.083
ALC	>1.1 $x10^3/\mu L$	107(96.4)	4(3.6)	1	1	
	≤1.1 $x10^3/\mu L$	71(55)	58(45)	21.85(7.59–62.86)	12.93(3.39–49.35)	0.0001*
NLR	<9.47	145(95.4)	7(4.6)	1	1	
	>9.47	33(37.5)	55(62.5)	34.5(14.42–82.6)	4.73(1.19–18.77)	0.027*
HGB	>13mg/dl	102(76)	20(16.4)	1	1	
	<13mg/dl	76(64.4)	42(35.6)	2.81(1.53–5.18)	3.50(1.15–10.62)	0.027*
Creatinine	<1.1mg/dl	164(78.1)	46(21.9)	1	1	
	>1.2mg/dl	12(50)	12(50)	3.56(1.50–8.46)	3.48(0.61–19.76)	0.158
AST/GOT	<40 Iu/l	108(77.7)	31(22.3)	1	1	
	>40 Iu/l	67(70.5)	28(29.5)	1.45(0.80–2.64)	1.63(0.58–4.53)	0.346

Notes: Data are expressed as n (%).1= reference. *p-value <0.05(on multivariable analysis).
Abbreviations: ALC, absolute lymphocyte count; ALP, alkaline phosphatase; ANC, absolute neutrophil count; AOR, adjusted odds ratio; DBP, diastolic blood pressure; CI, confidence interval; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; COR, crude odds ratio; GPT, glutamic oxaloacetic transaminase; GPT, glutamic pyruvic transaminase; HIV, human immunodeficiency virus; NLR, neutrophil to lymphocyte ratio; PR, pulse rate; RR, respiratory rate; SBP, systolic blood pressure; SO_2, oxygen saturation.

COVID-19 Care Center in Ethiopia from August 1 to October 30, 2021. Out of 240 patients studied, almost half of the patients (116, 48.3%) had severe disease, and the rest 124 (51.6%) had non-severe disease. Regarding the disease outcome, we found that a quarter of patients (25.8%) died, and 178(74.2%) were discharged alive.

Based on the ROC curve analysis, the optimal cutoff level of NLR for mortality was 9.47, which is concordant with the retrospective observational studies of Romania and Iran where the optimal cutoff values were 9.1 and 9.0, respectively. However, our result is slightly higher than 7.9 and lower than the 11.75 of two studies done in China.[20–23]

Table 7 Bivariable and Multivariable Analysis for Risk Factors Associated with Severity of Disease with COVID-19 (n=240)

Variables		Severity		COR(95% CI)	AOR(95% CI)	P-value
		Non-Severe n(%)	Severe n(%)			
Age	<65	101(57.7)	74(42.3)	1	1	
	≥65	23(35.4)	42(64.6)	2.49(1.38–4.49)	1.34(0.54–3.32)	0.521
Comorbidity	NO	55(57.9)	40(52.1)	1	1	
	YES	69(47.6)	76(52.4)	1.51(0.88–2.55)	0.39(0.10–1.42)	0.154
HTN	NO	86(59.3)	59(40.7)	1	1	
	YES	38(40)	57(60)	2.18(1.29–3.70)	1.95(0.69–5.52)	0.206
DM	NO	89(56.7)	68(43.3)	1	1	
	YES	35(42.2)	48(57.8)	1.79(1.04–3.07)	1.05(0.38–2.92)	0.919
Malignancy	NO	119(50.9)	115(49.1)	1	1	
	YES	5(83.3)	1(16.7)	0.20(0.02–1.79)	0.35(0.01–7.37)	0.505
SBP	NO	100(55.6)	80(44.4)	1	1	
	YES	24(40)	36(60)	1.87(1.03–3.39)	2.36(0.84–6.59)	0.100
DBP	NO	118(53.6)	102(46.4)	1	1	
	YES	6(30)	14(70)	2.69(1.00–7.28)	0.85(0.20–3.51)	0.828
WBC	<4.5, 4.5–11	110(62.5)	66(37.5)	1	1	
	>11 x10^3/µL	14(21.9)	50(78.)	16.83(6.14–46.14)	1.32(0.45–3.85)	0.611
HGB	>13mg/dl	61(50)	61(50)	1	1	
	<13mgldl	63(53.4)	55(46.6)	1.08(0.52–1.45)	0.55(0.24–1.28)	0.169
ANC	<6.5 x10^3/µL	91(74)	32(26)	1	1	
	>6.5 x10^3/µL	33(28.2)	84(71.8)	7.23(4.09–12.79)	2.69(0.94–7.64)	0.063
ALC	>1.1 x10^3/µL	87(78.4)	24(21.6)	1	1	
	<1.1 x10^3/µL	37(28.7)	92(71.3)	9.01(4.98–16.28)	3.03(1.07–8.53)	0.036*
NLR	<5.86	93(91.2)	9(8.8)	1	1	
	>5.86	31(22.5)	107(77.5)	35.67(16.14–78.70)	12.98(3.84–43.80)	0.0001*
AST/GOT	<40lu/l	86(61.9)	53(38.1)	1	1	
	>40 lu/l	36(37.9)	59(62.1)	2.65(1.55–4.55)	2.66(1.10–6.41)	0.028*
ALT/GPT	<40lu/l	94(56.6)	72(43.4)	1	1	
	>40 lu/l	26(39.4)	40(60.6)	2.00(1.12–3.59)	1.09(0.42–2.87)	0.849
Urea	<20mg/dl	37(71.2)	15(28.8)	1	1	
	>20mg/dl	87(46.5)	100(53.5)	2.83(1.45–5.51)	1.14(0.41–3.13)	0.798

Notes: Data are expressed as n (%). 1= reference. *p-value <0.05(on multivariable analysis).

Abbreviations: ALC, absolute lymphocyte count; ALP, alkaline phosphatase; ANC, absolute neutrophil count; AOR, adjusted odds ratio; DBP, diastolic blood pressure; CI, confidence interval; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; COR, crude odds ratio; GPT, glutamic oxaloacetic transaminase; GPT, glutamic pyruvic transaminase; HIV, human immunodeficiency virus; NLR, neutrophil to lymphocyte ratio; PR, pulse rate; RR, respiratory rate; SBP, systolic blood pressure; SO_2, oxygen saturation.

Table 8 Impact of NLR Cut-off Value (5.86) on Serious Clinical Outcome, ICU Admission and Usage Invasive Ventilation Among COVID-19 Patients at MCCC, Addis Ababa, Ethiopia, 2021

Variables		NLR Cut-Off for Severity		P value
		NLR <5.86 n (%)	NLR >5.86 n (%)	
ICU admission	Yes	14(13.7)	111(80.4)	<0.001
	No	88(86.3)	27(19.6)	
Invasive ventilation usage	Yes	3(2.9)	57(41.3)	<0.001
	No	99(97.1)	81(58.7)	
Shock	Yes	3(2.9)	52(37.7%)	<0.001
	No	99(77.1)	86(62.3)	
Complication	Yes	4(3.9)	67(48.6)	<0.001
	No	98(96.1)	71(51.4)	

Notes: Data are expressed as n (%). P values were calculated by χ^2 test.
Abbreviations: ICU, Intensive care unit; NLR, neutrophil to lymphocyte ratio.

Regarding the severity of the disease, we suggested an NLR of 5.86 as an optimal cut-off value for severity, which is in line with one study done in China,[24] and nearly close to two reports from Iran and China that had cut-off values of 6.5 and 4.5, respectively.[21,25] However, the value was higher than 3.3, 3.13, and 4.06 in three different studies from China,[26–28] This difference might be attributed to the use of different dependent variables, such as the likelihood of admission to an ICU, developing shock, and the likelihood of undergoing intubation, were used to define severe COVID-19 that might produce different cut off values among studies.

In addition, this variation might indicate that absolute NLR values measured in different populations are hardly comparable, optimal cut-off values may vary from one population to another, and a lack of data on the reference range in a specific population may also contribute to these differences. Therefore, determining the cut-off value is essential for NLR to be used in clinical settings specific to a specific locality.

The current study identified an NLR cutoff value of 9.47 for mortality with demonstrated sensitivity and specificity of 88.7% and 95.4%, respectively, and the positive predictive value was 62.5% while the negative predictive value was 95.4%. This is near to the pooled sensitivity (83%) and pooled specificity (83%) of a meta-analysis of ten studies involving 2967 patients with a cut-off value of 6.5.[29]

When we compared it with the previous studies, the Romania study recommended 9.1 as a cut-off value for NLR with 70% sensitivity and 67% specificity for mortality.[23] Two studies performed a ROC analysis to determine the optimal cutoff value of 11.75 with a sensitivity of 97.5% and a specificity of 78.1%,[20] and another study provided a cut-off value of 7.945 with a sensitivity of 65.3% and a specificity of 90.6%.[22] This narrow range of variability might be due to different optimal cut-off values used in different literature, different conditions of patients, or different comorbidities among the included study subjects.

The present study also revealed that the NLR of 5.86 cut-off value for the severity of disease with sensitivity and specificity of NLR was 92.2% and 75%, respectively, with PPV of 75.5% and NPV of 91%. This is consistent with the pooled specificity (78%), but higher sensitivity value than the pooled sensitivity (78%) of the meta-analysis of thirteen studies involving 1579 patients at a cut-off value of 4.5.[29]

Similarly, retrospectively analyzed clinical data from China revealed that an optimal threshold of 4.79 with a sensitivity of 83.9% and a specificity of 75% is in line with our study, with some narrow range difference in sensitivity.[30] This gap might be related to the use of different cut-off values and the condition of the patient.

Based on the multivariable logistic regression analysis at a 5% level of significance, the risk of in-hospital death was 4.73 times higher in patients with NLR ≥9.47 than in those patients having NLR of <9.47 with 95% CI, 1.19–18.78, P=0.027. This odds ratio falls in the range between 1.8 and 44 of the odds of mortality that were reported in previous studies at different cut-off values.[20,31–33] In addition, it is nearly comparable with a report from a meta-analysis which revealed that the odds of mortality increased by 2.74 fold in patients with elevated NLR than in those with normal NLR.[34]

Correspondingly, COVID-19 patients with an NLR of 5.86 on admission had significantly higher odds of severe disease as well as a strong prognostic factor for increased morbidity with an adjusted odds ratio ((AOR) of 12.98, 95% CI, 3.85–43.80; P 0.001). This is in line with the diagnostic odds ratio (DOR) of 13 with a cut-off value of 4.5 and it is closely related to the DOR of 11.45 with a cut-off value of 3.63 in two meta-analyses that included 13 and 10 articles, respectively.[31,35] The predicting potential of NLR in disease morbidity further also corroborated by our subgroup analysis on emphasizing that NLR >5.86 is independently associated with ICU admission, usage of invasive mechanical ventilation and development of complication which is almost in parallel with previous studies done Iran, China, Pakistan, Louisiana, Italy and Sri Lanka with an acceptable range of cut-off point from 3.13–6.5 across the respective studies.[21,27,36–39] This persistent association might be due to the pathogenesis of SARS CoV that results in extensive infiltration of neutrophils in the lung and increased neutrophils in the peripheral blood, and with growing evidence of a decrease in lymphocyte numbers by SARS CoV virus due to increased pro-inflammatory mediators that bind to lymphocytic surface receptors and subsequently initiate lymphocytic apoptosis, leading to lymphopenia that predisposes severe COVID-19 patients to cytokine storm, thus leading to more lymphocytic apoptosis and multi-organ failure.[27,31,34,35]

The results of this study have several clinical implications and strengths. Our data confirms and expands previous results in COVID-19 patients and emphasizes the relevance of routine hematologic tests and provided a simple way to determine the poor prognosis of patients with COVID-19, which is conducive to the allocation of medical resources in our limited resource setup. There are several limitations to the study:

1. Due to the single-center and retrospective nature of the study design, the real value of the NLR might be underestimated or overestimated in predicting poor prognosis,
2. Since all subjects in our study were hospitalized and diagnosed with COVID-19, the results of this study might not be directly applicable to other ambulatory patients.
3. Although we have adjusted for multiple potential confounders, residual and unmeasured confounders such as smoking history, BMI, coagulation predictors, and prior exposure of patients to different medications like steroids, were missed from patient records due to the retrospective nature of the study.
4. We only analyzed NLR at admission. However, there may be a need for serial monitoring of NLR throughout the disease course and its response to different treatment strategies, which could have more specificity in predicting mortality and severity of the disease.
5. Our study lacked a comparison of NLR with other well-known inflammatory markers like CRP and D-dimer.

Conclusions

NLR is a simple inflammatory biomarker that reflects the presence of systemic inflammation and is easily calculated at admission. An NLR greater than 9.47 was found to be a predictor of COVID-19 mortality, and an NLR greater than 5.86 was found to be a predictor of the severe form of COVID-19. Values above these thresholds were significantly associated with all-cause of COVID-19 mortality and the severity of the disease, respectively. It provides an objective input for early decision-making in the patient's management and allocation of limited resources like mechanical ventilation.

Abbreviations

ALC, absolute lymphocyte count; ALP, alkaline phosphatase; ANC, absolute neutrophil count; AOR, adjusted odds ratio; CI, confidence interval; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; COR, crude odds ratio; COVID 19, Corona virus diseases 19; DBP, diastolic blood pressure; GPT, glutamic oxaloacetic transaminase; GPT, glutamic pyruvic transaminase; HIV, human immunodeficiency virus; MCCC, millennium covid-19 care center; NLR, neutrophil to

lymphocyte ratio; NPV, negative predictive value; PPV, positive predictive value; PR, pulse rate; RR, respiratory rate; SARS COV2, severe acute respiratory syndrome coronavirus 2; SBP, systolic blood pressure; SO_2, oxygen saturation.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no conflicts of interest in relation to this work.

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