Am J Blood Res 2023;13(4):117-129
www.AJBlood.us /ISSN:2160-1992/AJBR0151500

Original Article

Hematological parameters and their predictive value for assessing disease severity in laboratory-confirmed COVID-19 patients: a retrospective study

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Received May 30, 2023; Accepted August 7, 2023; Epub August 15, 2023; Published August 30, 2023

Abstract: Background: The coronavirus disease 19 (COVID-19) infection has spread globally and caused a substantial amount of mortality and morbidity. Early detection of severe infections will improve care and reduce deaths. The use of hematological parameters in predicting COVID-19 disease severity, patient outcomes, and early risk stratification is limited. Therefore, the study was aimed at determining hematological parameters and their predictive value for assessing disease severity in laboratory-confirmed COVID-19 patients in Northwest Ethiopia. Methods: A retrospective cross-sectional study was conducted at the University of Gondar comprehensive specialized hospital and Tibebe Ghion comprehensive specialized referral hospital on 253 patients diagnosed with COVID-19 and admitted between March 2021 and February 2022. Data were extracted, and entered into Epi-data 4.2.0.0, and analyzed using SPSS version 25 software. Hematological parameters were provided as the median and interquartile range (IQR). Categorical variables were represented by their frequency, and the χ^2 test was applied to compare observed results with expected results. The receiver-operating curve (ROC) was used to establish the predictive value of hematological parameters for COVID-19 severity. A p-value < 0.05 was considered statistically significant. Results: On a total of 253 patients, there were 43.87% severe cases, with a mortality rate of 26.9%. The ROC analysis showed the optimal cutoff values for hematological parameters were ANC (3370), lymphocyte (680), NLR (9.34), PLR (290.77), platelets (332,000), and WBCs (4390.65). The area under the curve (AUC) values for NLR (0.679) and ANC (0.631) were high, with the highest sensitivity and specificity, and could potentially be used to predict COVID-19 severity. Conclusion: This study proved that high NLR and high ANC have prognostic value for assessing disease severity in COVID-19. Thus, assessing and considering these hematological parameters when triaging COVID-19 patients may prevent complications and improve the patient's outcome.

Keywords: COVID-19, hematological parameters, prognostic value, disease's severity

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the cause of the coronavirus disease 2019 (COVID-19) [1, 2]. SARS-CoV-2 is a positive-sense single-stranded RNA virus that is contagious in humans [3]. Despite the fact that all countries take significant diagnostic, therapeutic, and preventive steps at varying levels, SARS-COV-2 infection remains the leading cause of death globally [4]. In all nations of the world, the epidemic has created a significant health, economic and social burden, but more so in developing countries [5]. Many different methods are used around the world for COVID-19 infection prevention and treatment, but they are still not completely effective [6, 7].

COVID-19 is a systemic infection with symptoms in the cardiovascular, pulmonary, gastrointestinal, neurological, and hematological systems [8, 9]. For COVID-19 patients who are hospitalized, laboratory tests with serial blood counts are essential for early prediction in assessing severity and evaluating prognosis [10]. The hematological parameters and inflamma-

tory indexes are associated with severe illness in COVID-19 patients. COVID-19 can cause significant cytopenia, mainly severe lymphopenia and excessive exhaustion of CD8+ T cells, resulting in an immunocompromised state and a cytokine storm [11]. Different studies revealed that when the condition of COVID-19 infections worsens, numerous hematological abnormalities can be noticed, many of which are warning signs for very bad clinical outcomes [12, 13].

The frequent hematological abnormalities in COVID-19 include changes in platelet count, white blood cells (WBC), hemoglobin, coagulation/fibrinolytic alterations, lymphopenia, and high D-dimer levels [14]. Low lymphocyte, high neutrophil, low platelet, and coagulation-related issues are the most frequent hematological disorders [15-17]. Understanding the hematological characteristics of individuals with COVID-19 may aid in early triaging and patient severity prediction [10, 15, 16]. A high WBC count, neutrophil count, neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR), and a low lymphocyte count are the hematological profiles that will aid in the early prediction of the severity of COVID 19 patients [18-20]. Several studies confirmed that the NLR and PLR are reliable hematological indices to predict the severity of COVID-19 diseases [18, 21].

Research on the hematological features of COVID-19 patients in Ethiopia is limited. A study in Addis Ababa, Ethiopia, showed total cytopenia of 41%, while lymphopenia was present in 72.2%. Severe cytopenia was more common in patients with severe symptoms than in those with moderate disease conditions [22]. Another study in Debre Markos Isolation and Treatment Center, Ethiopia, found that leukocytosis, mainly granulocytosis and monocytosis, and lymphopenia were the predominant hematological abnormalities in COVID-19 patients [23]. Besides, a retrospective study by Ayalew *et al.* confirmed that the values of absolute neutrophil count (ANC), NLR, and PLR were higher in the severe COVID-19 cases than in the non-severe group [19].

Although multiple studies have shown that hematological parameters are frequently affected in individuals who experience severe disease, there are currently no recommended test values that help in diagnosing severe disease early [20, 24, 25]. A better patient outcome may result from an earlier diagnosis of the disease's severity based on these hematological tests. Because Ethiopia has limited resources, employing common laboratory tests like the complete blood count (CBC) to predict the severity of the diseases can aid in triaging the patient and improve the standard of care. Therefore, the current study was aimed at determining the hematological parameters and their predictive value for assessing disease severity in laboratory confirmed COVID-19 infection at the University of Gondar comprehensive specialized hospital and Tibebe Ghion comprehensive specialized referral hospital.

Methods and materials

Study design, period and area

An institutional-based retrospective cross-sectional study was conducted by reviewing the medical charts of COVID-19 patients from March 2021 to February 2022. The study was conducted both at the University of Gondar comprehensive specialized hospital and Tibebe Ghion comprehensive specialized referral hospital. The University of Gondar's comprehensive specialized hospital provides COVID-19 treatment and diagnosis services for COVID-19-suspected and infected patients. The hospital has a separate ward where patients who have been admitted with COVID-19 are treated. Tibebe Ghion comprehensive specialized referral hospital is located in Bahir Dar, the capital of the Amhara Regional State. The COVID-19 treatment center is located in a separate building within the hospital, and its staff member's alternate shifts between the hospital and the COVID-19 center.

Population and eligibility criteria

The study population was all laboratory-confirmed COVID-19 patients who had complete follow-up data at the University of Gondar comprehensive specialized hospital and Tibebe Ghion specialized referral hospital during the study period. All laboratory-confirmed COVID-19 patients aged 18 years and older who have

a complete blood count result in their medical records were included in the study. However, COVID-19 patients with known cytopenia due to diseases other than COVID-19, patients on chemotherapy for known malignancy before COVID-19 confirmation, and those who have no complete laboratory results in their medical records were excluded from the study.

Sample size and sampling procedure

All laboratory-confirmed COVID-19 patients who had complete follow-up data on key hematological and clinical variables in their medical records were included in this study. A total of 253 patients, 103 from the University of Gondar comprehensive specialized hospital and 150 from Tibebe Ghion comprehensive specialized referral hospital, were included.

Variables

Severe COVID-19 infection was the dependent variable of the study. The independent variables of the study were socio-demographic variables, including age, sex, marital status, and residency; medical comorbidities, including diabetes mellitus, chronic lung diseases, cardiac disease, liver disease, HIV, and renal disease; clinical parameters, including respiratory rate, oxygen saturation, mechanical ventilator requirement, and patient outcome, including recovered, dead, and against.

Operational definition

Mild: Patients with an uncomplicated upper respiratory tract viral infection may have symptoms such as fever, fatigue, and cough with or without sputum production, anorexia, malaise, muscle pain, sore throat, nasal congestion, headache, diarrhea, nausea, and vomiting; and loss of smell or taste [26].

Moderate: A patient with moderate illness has mild pneumonia but no hypoxemia or need for supplemental oxygen [26].

Severe: Severe illness is described as a patient having severe pneumonia, acute respiratory distress syndrome (ARDS), or sepsis. These are group of patients responding to non-invasive management manifesting with: dyspnea, RR ≥ 30/min or other features of severe respiratory distress, blood oxygen saturation (spo2) ≤ 90%, or when there is ABG pao2/fio2 ratio < 300 or when Kigali definition is used spo2/fio2 < 350, and/or lung infiltrates in CT imaging > 50% within 24 to 48 hours [26].

Critical: Respiratory failure, septic shock, and/or multiple organ dysfunctions necessitate invasive or special management [26].

Progression of the illness: Progression from mild to moderate, from moderate to severe, and from severe to critical COVID-19 infection.

Fully recovered: Absence of all the clinical symptoms.

Against: The patient leaves the treatment center against medical advice.

Data collection method and measurements

A pre-tested, structured data extraction sheet was prepared and adopted. Data on patients' socio-demographic variables, such as age, gender, and place of residence; type of comorbidities, such as diabetes, HIV, liver disease, renal disease, malignancy, and chronic lung diseases; hematological parameters at admission including red blood cells (RBC), hemoglobin, total white blood cell (WBC), absolute and relative lymphocyte count, absolute and relative neutrophil count, and platelet count, Neutrophil to lymphocyte ratio (NLR) and platelet to lymphocyte ratio (PLR); severity of COVID-19 infection; and patient outcomes were extracted from their medical records, which included separate ward registration, COVID-19 laboratory registration, and medical intensive care unit (ICU) registration books. The data was collected by two registered nurses after an explanation and brief training.

Data quality control

To ensure the quality of the data, data collectors were trained on the objective, relevance of the study, and confidentiality of the information. To check the validity and appropriateness of the questions, a pretest was undertaken.

Data analysis and interpretation

The investigators cleaned and checked the consistency of the data. Then it was coded,

entered into Epi-data 4.2.0.0, and exported to IBM SPSS software (version 25.0) for analysis. Frequency, tables, and graphs were used to summarize the results. The Shapiro-Wilk test was used to determine whether the data were normal. The hematological parameters were presented as the median and interquartile range (IQR). The Wilcoxon-matched-pairs signed test was done to evaluate differences in the hematological parameters between groups. The categorical variables were represented by their frequency, and the χ^2 test was used for comparisons. The receiver-operating curve (ROC) analysis was utilized to establish the ideal cut-off values of hematological parameters that predict COVID-19 severity. And those with a *P*-value less than 0.05 were considered significant.

Ethical consideration

The study protocol was approved by the ethical review board of the School of Medicine, College of Medicine and Health Science, University of Gondar (Ref. No: SOM/1651/14). Besides, an additional support letter was obtained from the chief executive officer of the hospitals. The ethical review committee waived the requirement for patient consent because the data were obtained from medical records. Other than for the research's stated purposes, the information collected from the patient's medical records was not used. Through the use of codes in an anonymous data collection method, data confidentiality was guaranteed.

Results

Socio-demographics and medical histories of study participants

A total of 253 medical records of COVID-19 patients were reviewed and included in this study. The mean age of the patients was 56.82±18.5 (SD) years, and 67.6% were male. More than half (62.8%) of them were urban residents. Comorbid conditions affect 37.9% of patients, with diabetes mellitus (17.39%), HIV/AIDS (7.91%), and chronic lung disease (7.91%) accounting for the highest percentages. The proportion of severe COVID-19 cases was 43.87%. During their admission period, more than half of the patients (52.3%) experienced severity progression. Only 7.1% of patients underwent mechanical intubations. More than two-thirds of the patients (71.9%) recovered before being discharged. However, the mortality rate was 26.9%. About 66.8% of patients came to the hospital ≤ 7 days after the onset of symptoms. Around 43.9% of patients were hospitalized for more than seven days. Additionally, 39.9% of patients had oxygen saturation levels below 90 (**Table 1**).

Hematological profiles of COVID-19 patients

The median (IQR) WBC values of severe COVID-19 patients were 7900 (6500) cells/dl, which is higher than the values of non-severe patients and the normal range. The median (IQR) value of ANC was 6220 (6147.05) cells/dl, which is higher than in non-severe patients. Further, the median (IQR) NLR and PLR values of severe patients were 10.41 (14.18), 242.58 (285.50), and respectively, these values are higher than those of non-severe patients. However, the lymphocyte count, platelet count, and hemoglobin level were 700 (739.6) cells/dl, 181000 (134000) cells/dl, and 13.3 (3.4) g/dl, respectively, which are all lower than those of non-severe patients (**Table 2**).

Comparison of hematological and clinical parameters by diseases severity

In the current study, neutrophil counts were significantly higher in the severe group than in the non-severe group (P = 0.001). Besides, the WBC count remains significantly higher in the severe patients (P = 0.002). In terms of oxygen saturation level, the maximum number of severe COVID-19 patients had a low (< 90) oxygen level, which is statistically significant (P = 0.001). However, there was no significant correlation between other hematologic profiles and the severity of COVID-19 (**Table 3**).

Comparison of hematological and clinical parameters by patient's outcome

The median (IQR) age of non-survivors was significantly higher (68 (22.5)) than the survivor group (55 (29) years) (P = 0.0001). The median WBC count of non-survivors (8940 (9345) cells/dl) was higher than that of survivors (6400 (5590) cells/dl), which is statistically significant (P = 0.001). Besides, there are high ANC (7588.4 (9410)) cells/dl and neutrophil percent (88.8 (13.55%)), PLR (301.97 (318.38)), and NLR (13.85 (17.18)) values

Table 1. Socio-demographic and clinical characteristics of COVID-19 infected patients

Characteristics	Categories	Frequencies	Percentage
Age in years (mean ± SD)	-	56.82±18.5	-
Sex	Male	171	67.6
	Female	82	32.4
Marital status	Currently married	74	29.2
	Unmarried	24	9.5
	Status unknown	155	61.3
Residence	Urban	159	62.8
	Rural	94	37.2
Comorbidities	Yes	96	37.9
	No	157	62.1
Types of comorbidities	DM	44	17.39
	HIV/AIDS	20	7.91
	Cardiac diseases	18	7.11
	Chronic lung disease	20	7.91
	Renal disease	10	3.95
	Liver	3	1.19
Severity of the illness at initial diagnosis	Non-severe	142	56.13
	Severe	111	43.87
Progression of the illness during admission period	Progression to severity	133	52.3
	No Progression	120	47.4
Was the patient on mechanical intubation	Yes	18	7.1
	No	235	92.9
Outcome of the patient at discharge	Recovered	182	71.9
	Against	3	1.2
	Dead	68	26.9
Onset of illness	≤ 7 days	169	66.8
	8 to 14 days	74	29.2
	> 14 days	10	4.0
Oxygen saturation level	< 90	152	60.1
	≥ 90	101	39.9
Duration of admission	≤ 7 days	142	56.1
	> 7 days	111	43.9

among non-survivors, which are statistically significant at P = 0.01. Absolute lymphocyte count and percent are lower in non-survivor patients. However, there is no significant difference between survivors and non-survivors in the number of platelets or hemoglobin. Moreover, the outcomes of patients did not differ among comorbidities or sexes (**Table 4**).

Hematological parameters and predictive values of COVID-19 diseases

To use the optimum cut-off values of laboratory results to discern severe from non-severe COVID-19 infection, we analyzed the optimal cut-off values calculated by the ROC analysis. As a result, the ANC, lymphocyte, NLR, PLR, platelet counts, and WBC had AUCs of 0.63, 0.62, 0.68, 0.58, 0.51, and 0.60, respectively. The optimal cutoff values for ANC (3370 cells/dl), lymphocyte (680 cells/dl), NLR (9.34), PLR (290.77), platelet (332000 cells/dl), and WBC (4390.65 cells/dl) represent the maximum of sensitivity and specificity. NLR, absolute neutrophil, and lymphocyte counts had higher AUC values (0.68, 0.63, and 0.62, respectively) and were conducive to distinguishing severe patients with COVID-19. Thus, NLR and absolute neutrophils were considered the most reliable parameters for the early prediction of COVID-19

Table 2. Hematological profiles of severe and non-severe COVID-19 patients

Hematological parameters	Unit of measurement	Normal range	Severity	
			Non-severe Median (IQR)	Severe Median (IQR)
WBC	Count/dl	3,600-10,200/dl	6280 (5960)	7900 (6500)
Lymphocyte count	Count/dl	1,000-3,200/dl	884.4 (710)	700 (739.6)
Lymphocyte percent	Percent	15.2-43.3%	15.8 (17)	8.3 (11.9)
ANC	Count/dl	1,700-7,600/dl	4762.8 (5380.4)	6220 (6147.05)
Neutrophil percent	Percent	43.5-73.5%	75.6 (20.3)	86.1 (16.2)
Platelet	Count/dl	152,000-433,000/dl	191500 (124000)	181000 (134000)
Hemoglobin	Gram/dl	12.5-16.3 gram/dl	13.5 (3.1)	13.3 (3.4)
NLR	Ratio	-	4.78 (7.45)	10.41 (14.18)
PLR	Ratio	-	200.40 (163.75)	242.58 (285.50)

Abbreviations: WBC, White blood cell; ANC, Absolute Neutrophil Count; NLR, Neutrophil to Lymphocyte Ratio; PLR, Platelet to Lymphocyte Ratio; IQR, Interquartile Range.

Table 3. Comparisons of the clinical and hematological profiles of the patients by diseases severity level using chi square test

Variables	Categories	Severity status			*P*-value
		Non-severe	Severe	Total	
ANC	High	64 (25.30)	67 (26.48)	131 (51.78)	0.001**
	Normal	41 (16.21)	35 (13.83)	76 (30.04)	
	Low	37 (14.62)	9 (3.56)	46 (18.18)	
WBC	High	35 (13.83)	37 (14.62)	72 (28.46)	0.002**
	Normal	80 (31.62)	69 (27.27)	149 (58.89)	
	Low	27 (10.67)	5 (1.98)	32 (12.65)	
Platelet	High	12 (4.74)	13 (5.14)	25 (9.88)	0.67
	Normal	80 (31.62)	59 (23.32)	139 (54.9)	
	Low	50 (19.76)	39 (15.42)	89 (35.18)	
Hemoglobin	Normal	86 (33.99)	63 (24.90)	149 (58.89)	0.55
	Low	44 (17.39)	41 (16.21)	85 (33.60)	
	High	12 (4.74)	7 (2.77)	19 (7.51)	
Lymphocyte count	Low	91 (35.97)	81 (32.02)	172 (67.9)	0.29
	Normal	46 (18.18)	26 (10.28)	72 (28.46)	
	High	5 (1.98)	4 (1.58)	9 (3.56)	
Oxygen saturation level	< 90	67 (26.48)	85 (33.60)	152 (60.0)	0.001**
	≥ 90	75 (29.64)	26 (10.28)	101 (39.9)	
Onset of illness	≤ 7 days	94 (37.15)	75 (29.64)	169 (66.8)	0.95
	8 to 14 days	42 (16.60)	32 (12.65)	74 (29.25)	
	> 14 days	6 (2.37)	4 (1.58)	10 (3.95)	
Duration of admission	≤ 7 days	86 (33.99)	56 (22.13)	142 (56.1)	0.10
	> 7 days	56 (22.13)	55 (21.74)	111 (43.8)	

Note: **indicates P < 0.01. Abbreviations: WBC, White blood cell; ANC, Absolute Neutrophil Count.

severity. However, platelets could not be used as a potential diagnostic biomarker for predicting disease severity (P = 0.8380), they had a lower AUC value, and their sensitivity and specificity were 84.68% and 9.15%, respectively (**Figure 1** and **Table 5**).

Discussion

In this retrospective study, the incidence of severe COVID-19 case was 43.9% (95% CI, 37.8-50.1). The findings of the study were in line with a study done in Addis Ababa, Ethiopia

Table 4. Spearman's and chi-square tests to show the tabulation of demographic, clinical and hematological profiles with patient outcome

Variables		Patients' outcome		*P*-value
		Survivor	Non-survivor	
Age	Median (IQR)	55 (29)	68 (22.5)	0.0001**
Comorbidity	Yes	69	27	0.726
	No	116	41	
Sex	Male	123	48	0.537
	Female	62	20	
WBC	Median (IQR)	6400 (5590)	8940 (9345)	0.0052**
Lymphocyte count	Median (IQR)	900 (770)	603.6 (440)	0.001**
ANC	Median (IQR)	4820 (5180)	7588.4 (9410)	0.001**
Lymphocyte percent	Median (IQR)	15.4 (16)	5.9 (6.15)	0.001**
Neutrophil percent	Median (IQR)	77.2 (19.4)	88.8 (13.55)	0.001**
Platelet (count/dl)	Median (IQR)	193000 (125000)	172500 (144500)	0.2976
Hemoglobin (g/dl)	Median (IQR)	13.6 (3.1)	12.7 (3.05)	0.0694
NLR	Median (IQR)	4.801 (7.65)	13.848 (17.18)	0.001**
PLR	Median (IQR)	193.612 (166.211)	301.97 (318.376)	0.002**
Mechanical intubation	Yes	4	14	0.001**
	No	181	54	

Note: **indicates P < 0.01. Abbreviations: WBC, White blood cell; ANC, Absolute Neutrophil Count; NLR, Neutrophil to Lymphocyte Ratio; PLR, Platelet to Lymphocyte Ratio; IQR, Interquartile Range.

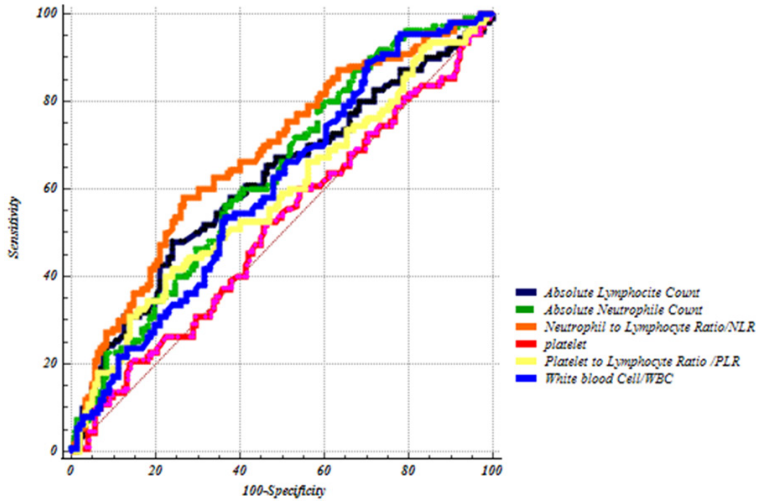

Figure 1. ROC curve analysis to indicate the diagnostic values of hematological profiles for distinguishing severe-patients with COVID-19.

(42.4%) [27]. However, the incidence of severe cases was lower than in previous studies conducted at different COVID-19 treatment centers [10, 15]. Besides, the mortality due to COVID-19 was 26.9% in this study, which is similar to the finding of a previous study conducted in Debre Markos Ethiopia (28.68%) [23]. This outcome is high compared to a study in Iran (13.9%) [15]. The high proportion of severe COVID-19 cases might be a possible reason for the high mortality in the current study. This difference might be due to the fact that most non-severe patients do not seek medical attention or to cytokine and immunological factors.

The median (IQR) age of non-survivors was significantly older (68 (22.5)) than the survivor group (55 (29)) years. The finding of the study is supported by a previous study conducted in Wuhan, which stated that a unit increase of age could increase the severity of COVID-19 by 2.52 [28]. This might be due to the fact that as age increases, the risk of acquiring chronic medical conditions such as cardiovascular disease, diabetes, digestive system disease, and other chronic disease increases, similar to previous viral infections such as influenza A [29, 30]. The median time from initial onset of symptoms to admission was 7 days,

Table 5. The predictive value of hematological parameters for the severity of COVID-19 cases

Hematological parameters	Optimal cut-off value	AUC 95% CI	Sensitivity (%)	Specificity (%)	*P*-value
ANC (cells/dl)	> 3370	0.63 (0.57-0.69)	87.39	33.10	0.0002**
Lymphocyte count (cells/dl)	≤ 680	0.62 (0.56-0.68)	48.65	99.97	0.0008**
NLR	> 9.34	0.68 (0.62-0.73)	58.18	73.24	< 0.0001**
PLR	> 290.77	0.58 (0.52-0.64)	41.82	76.06	0.0241**
Platelet (cells/dl)	≤ 332000	0.51 (0.45-0.57)	84.68	9.15	0.8380
WBC	> 4390	0.60 (0.54-0.67)	29.58	89.19	0.0036**

Note: **indicates P < 0.001. Abbreviations: WBC, White blood cell; ANC, Absolute Neutrophil Count; AUC, Area Under the Curve; CI, Confidence Interval; NLR, Neutrophil to Lymphocyte Ratio; PLR, Platelet to Lymphocyte Ratio.

which was similar to previously reported studies in China [31, 32]. In another study, the median time from symptom onset to severe hypoxemia and ICU admission was approximately 7-12 days [33]. Most non-survivor patients are on mechanical intubation as compared to survivor patients. The finding was consistent with the results of a previous study, which reported that out of 1966 COVID-19 patients, 61% died within 28 days after intubation [34].

The median (IQR) of the total WBC count of non-survivors was 8940 (9345) cells/dl, which is higher than that of survivors 6400 (5590) cells/dl (P = 0.0052). According to several studies, patients with severe outcomes from COVID-19 have a consistently increased WBC count [27, 35, 36]. A study by Zhu et al. confirmed that COVID-19 patients with elevated WBC are 1.14 times at a high risk of death [37]. Besides, the absolute lymphocyte count was significantly lower in non-survivors, while the ANC was significantly higher in the non-survivor group. The findings of the study were in agreement with the results of several studies conducted by *Henry et al.* [38], *Penaloza et al.* [39], and *Sukrisman et al.* [40]. Elevated ANC related to the cytokine storm and lymphopenia in severe cases of COVID-19 pneumonia and are associated with a poor prognosis [41]. Viral infections frequently involve the destabilization of balanced immune cell frequencies and numbers. This is brought on by and strengthens viral immune evasion and survival [42]. Studies have shown that the T-lymphocyte subsets, particularly T-helper and T-suppressor cells, are primarily responsible for the reduction in lymphocytes, and the prevalence of lymphopenia in COVID-19 patients suggests severe tissue injury and inflammation [40, 43]. An increased inflammatory response, which results in increased granulocyte production but lymphocyte apoptosis, is the alternative explanation that could explain lymphopenia [44].

The PLR showed a higher value in non-survivors than survivors (193.61 vs. 301.97), but no difference between severe and non-severe COVID-19 cases. According to Simon et al., PLR has no role in predicting markers of severity but does predict mortality in COVID-19 patients [45]. A previous systematic review and meta-analysis study by *Sarkar et al.* concluded that a higher level of PLR on admission in COVID-19 patients is associated with increased morbidity and mortality [46]. PLR is an indicator of inflammation, and inflammation is central to the pathogenesis of COVID-19. The progression of inflammation or a dysfunctional immune response has been associated with severe COVID-19 disease and poor outcomes [47, 48].

The ROC analysis results revealed that a total WBC count > 4390 cells/dl with an AUC of 0.60 was an indicator of severity in our study. Similar findings were also reported by different scholars [10, 16, 49, 50]. However, findings from recent observational studies are inconsistent, and it is difficult to infer the causal role of WBC in severe COVID-19 due to confounding and reverse causation [9, 51, 52]. Most existing studies measure blood cell counts in patients with confirmed infection with SARS-CoV-2 and as a result, the hematological indices could have been modified by immune responses [53]. It is unknown if blood cell counts before infection are associated with the risk of developing severe COVID-19. Even if WBC are measured before infection, they are influenced by many exogenous and endogenous factors (e.g., age, gender, disease status, and medications), which will confound the observational associations [54, 55].

The ANC with a cutoff of > 3,370 cells/dl and an AUC of 0.63 has a significant role in predicting COVID-19 severity in this study. In a similar manner, lymphocyte count has a favorable prognostic value with a cutoff value of ≤ 680 and an AUC of 0.62 with a specificity of 99.97%. Levels of neutrophils have been suggested to reflect the inflammatory state during disease progression, while lymphocyte levels represent the outcome of controlled immune responses [56]. Severe illness following SARS-CoV-2 infection was associated with a higher neutrophil count and a lower lymphocyte count than mild infection [57]. Wang et al., also found that fatal cases of SARS-CoV-2 infection had increased neutrophil counts and decreased lymphocyte counts [58]. More recently, Liu *et al.* also observed decreased lymphocyte counts in patients with acute respiratory distress syndrome compared with those without acute respiratory distress syndrome [49].

The NLR with a cut-off value of > 9.34 and an AUC of 0.68, a specificity of 73.24% and a sensitivity of 58.18% seem to be good parameters in our investigation for early COVID-19 severity prediction. NLR demonstrated the largest AUC at 0.841, with the highest specificity (63.6%) and sensitivity (88%) when employed as a biomarker for differentiating severe COVID-19 patients, according to a study carried out in Wuhan [28]. Moreover, several studies indicated that NLR and PLR had significantly higher values in severe COVID-19 patients and confirmed that they have a predictive role [19, 43, 59].

The current study demonstrated PLR had an optimal cut-off value of > 290.77, with 76.06% specificity and 41.82% sensitivity, to be able to forecast the severity of COVID-19. The PLR at the time of platelet peak emerged as an independent prognostic factor for prolonged hospitalization in the multivariate analysis. It was suggested that a high PLR may indicate a more pronounced cytokine storm due to enhanced platelet activation [60]. A meta-analysis revealed that severe COVID-19 patients had greater PLR levels at admission compared to non-severe patients [61].

Platelets had a lower AUC (0.51) with a sensitivity (84.68%) and specificity (9.15%) that could not be used as a potential diagnostic biomarker for disease severity (P = 0.8380). There was no significant difference between survivors and non-survivors in the number of platelets. A similar study conducted in Iran revealed that there was an insignificant difference in platelet counts between severe and non-severe, survivors and non-survivors, and severe survivors and severe non-survivors groups at the time of admission to the hospital [15]. However, many other studies have reported that COVID-19 alters the platelet transcriptome [62-64]. Viral and bacterial infections are commonly associated with thrombocytopenia and alterations in platelet morphology [65]. A study by *Qu et al.* showed that among 30 hospitalized patients with COVID-19, those presenting with a peak in the platelet count during the disease course had worse outcomes. Inversely, other studies reported that a lower platelet count had been observed in patients with more severe COVID-19 [66-68].

The study has the following limitations: As this study is retrospective, the data may be incomplete or inconsistent, making it difficult to collect essential clinical and behavioural variables that could potentially limit the study's findings. Since the sample size of the study was small, it may reduce the generalizability of the findings. Furthermore, because the design is cross-sectional, it does not show dynamic changes in patients' hematological profiles or the precise associations between hematological changes and disease severity.

Conclusion

This study showed that high ANC and high NLR have better predictive values for severity in COVID-19 patients. Therefore, it is necessary to evaluate the hematological profiles of COVID-19 patients while triaging and assigning potential treatment modalities for COVID-19 patients. Because complete blood testing is inexpensive, these hematological parameters can be considered diagnostic and predictive biomarkers for the severity of COVID-19 in resource-limited settings.

Acknowledgements

We would like to acknowledge the Department of Internal Medicine at the University of Gondar for providing the funding and opportunity for this study. We would also like to thank the University of Gondar comprehensive special-

ized hospital and Tibebe Ghion comprehensive specialized referral hospital COVID-19 treatment center staff members for their cooperation and assistance during data collection.

Disclosure of conflict of interest

None.

Abbreviations

COVID-19, Coronavirus Disease 19; SARS-CoV-2, Severe Acute Respiratory Syndrome Coronavirus 2; HIV, Human Immunodeficiency Virus; NLR, Neutrophil to Lymphocyte Ratio; PLR, Platelet to Lymphocyte Ratio; WBC, White blood cell; ANC, Absolute Neutrophil Count; AUC, Area under the curve; CI, Confidence Interval; ROC, Receiver Operating Characteristic Curve; IQR, Interquartile Range.

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