

Can Hematological Ratios Predict Outcome of COVID-19 Patients? A Multicentric Study

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Introduction: Coronaviruses belong to a large family that leads to respiratory infection of various severity. Hematological ratios are indicators of inflammatory response widely used in viral pneumonia with affordability in developing countries.

Purpose: Study the role of the neutrophil lymphocyte ratio (NLR), derived NLR ratio (d-NLR), platelet lymphocyte ratio (PLR), and lymphocyte monocyte ratio (LMR) in predicting the outcome of COVID-19 Egyptian patients.

Methods: A retrospective study on 496 COVID-19 Egyptian patients, managed in four tertiary centers, grouped into non-severe, severe, and critical. Patients' laboratory assessment including total leucocyte count (TLC), absolute neutrophil count (ANC), absolute lymphocyte count (ALC), absolute monocyte count (AMC), NLR, d-NLR, LMR and, PLR were reported as well as C reactive protein (CRP), D-dimer and serum ferritin.

Results: TLC, ANC, AMC, NLR, d-NLR and, PLR were highest in the critical group ($p < 0.001$ for all except AMC $p = 0.033$), while this group had the least ALC and LMR ($p = 0.049$ and < 0.001 , respectively). Higher CRP and d-dimer levels were reported in the critical group ($p < 0.001$). At the same time, higher ferritin was found in the severe group more than the critical and non-severe groups ($p < 0.001$, $p = 0.005$, respectively). We calculated the optimal cut-off values of the hematological ratio; NLR (3.5), d-NLR (2.86), PLR (192), and LMR (3). D-NLR had the highest specificity (89.19%), while NLR had the highest sensitivity (71.38%). By univariate logistic regression, age, DM, HTN, cardiovascular diseases, COPD, NLR, d-NLR, LMR and PLR, CRP, steroid, oxygen aids, and mechanical ventilation were associated with the severity of COVID-19. Still, only age, NLR, CRP, and oxygen aid were independent predictors in multivariate logistic regression.

Conclusion: NLR is a predictor for severity in COVID-19. LMR, d-NLR, and PLR may assist in risk stratification.

Keywords: COVID-19, NLR, d-NLR, LMR, PLR, Egypt

Introduction

COVID-19 virus, a single-chain enveloped RNA virus,¹ causes multisystemic infections in animals and humans, mainly leads to respiratory tract infection.² Classically patients exhibit mild symptoms such as fever, sore throat, and upper respiratory tract infections.³ Severe respiratory tract infection that contributes to the syndrome of adult respiratory distress, multiple organ failure, and even death is reported, especially in the elderly and in patients with comorbidities.^{4,5} Declaring COVID-19 as a pandemic, serious morbidity, and mortality; created an urgency to study diagnostics, treatment, and prognostic markers.⁴

Inflammatory biomarkers representing the immune status are possible predictors of prognosis for COVID-19.⁵ Hematological ratio such as neutrophil to lymphocyte

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ratio (NLR), derived NLR ratio (d-NLR) (calculated by neutrophil count divided by the result of WBC count minus neutrophil count), platelet to lymphocyte ratio (PLR), and lymphocyte to monocyte ratio (LMR) are systemic inflammatory markers that have already been extensively investigated as a potential predictor of viral pneumonia.⁶ Such ratios are useful, inexpensive prognostic indicators that can be widely tested in developing countries with respectable significance in viral pneumonia, including COVID-19.^{6–8}

The diagnostic use of NLR in bacteria⁹ and viral pneumonia⁶ as well as in COVID-19 positive patients has been documented; the NLR is substantially greater in COVID-19 cases vs controls.⁸ NLR can be easily used as a rapid, inexpensive, available prognostic indicator.^{6,8} Both PLR and LMR are considered indicators of the systematic inflammatory response and useful predictors for the prognosis in viral pneumonia.¹⁰ More studies are demanded to decide the applicable threshold of d-NLR, PLR, and LMR and decide their predictive value.

This retrospective, multi-centric study was conducted to investigate the complete blood count parameters (NLR, d-NLR, PLR, and LMR) as inflammatory biomarkers and prognostic indicators in 496 COVID-19 positive cases.

Methods

Study Design

The study was a retrospective study, including 496 COVID 19 patients, diagnosed based on guidance from WHO with Positive SARS-CoV-2 RNA identification by real-time PCR methods in throat swab specimens.¹¹ The study included patients admitted to four major tertiary centers in Upper Egypt (Assiut University Hospital, El Rajhi Hospital, Aswan University Hospital, South Valley University Hospital) through June 2020.

Data of the Patients

Data of the patients were gathered from the hospital reports following the authorization of the local research ethics committee (IRB number: 17300513) according to the Declaration of Helsinki. It included: age, sex, history of smoking, diabetes, hypertension, chronic chest disease and cardiovascular disease, duration of hospital admission and outcome, treatment included steroid and oxygen supply either by low flow oxygen supplementation (nasal cannula, facial masks, or non-rebreather facial masks) or high flow oxygen supplementation (high flow nasal

cannula, continuous positive ventilation pressure (CPAP) or mechanical ventilation).

Investigations Included

Complete blood count; total leukocyte count (TLC), red blood cells, hemoglobin level, absolute lymphocyte count (ALC), absolute monocyte count (AMC), absolute neutrophil count (ANC), NLR (ANC/ALC), derived NLR ratio (d-NLR; calculated by ANC divided by the result of TLC count minus ANC), PLR (Platelet count/ALC) and LMR (ALC/AMC). Inflammatory markers; CRP (C-reactive protein) and serum ferritin and coagulation factor; D-dimer. All collected laboratory results are at the peak of the disease. Definition as the beginning of the symptoms that meet the categories of severity of illness as determined by WHO.^{12,13}

Computed tomography (CT) of the chest of the patients was classified into specific findings suggestive to COVID19 infection as bilateral or unilateral multifocal ground-glass opacities that classically predominate in the peripheral, posterior, and basal part of the lungs or other less specific findings. CORADS classification was scored from very low or CO-RADS 1 to very high or CO-RADS 6 based on the CT findings.

Patients were classified into the following categories of severity of illness:¹⁴

1) Critical: patients with any of the following criteria: respiratory failure that requires artificial ventilation, shock, or other organ damage that requires intensive care unit monitoring and treatment.

2) Severe: patients with a ratio of arterial partial oxygen pressure to inspired oxygen fraction ($\text{PaO}_2/\text{FiO}_2$) <300 mmHg, respiratory rate >30 breaths per minute, lung infiltrates $>50\%$, or patients with $\text{SpO}_2 <94\%$ in room air.

3) Non-severe: patients who did not meet the criteria of critical or severe illness.

All patients were treated according to the World Health Organization's provisional guidelines (WHO). All patients received steroids, and none of the patients received immunomodulatory drugs.^{2,11}

Statistical Analysis

SPSS version 25.0 was used for data management and data analysis. Quantitative variables were first subjected to the normality test (Kolmogorov v Smirnov). Continuous variables were presented median (interquartile range), and the Kruskal–Wallis test assessed their differences. Categorical variables were described as numbers (percentage) and were compared by the chi-square test and fisher's exact test. The

optimal cut-off values of the continuous NLR, d-NLR, PLR, and LMR were calculated using the receiver operating curve (ROC) analysis. The Kaplan–Meier survival analysis and COX regression analysis were used to investigate the independent adverse factors that might check patients' recovery and discharge with COVID-19. The demographics and laboratory data with significant differences between the three groups were assessed by univariate and multivariate logistic regression analysis to discover the independent early predictors and risk factors associated with the disease severity of COVID-19. A two-sided $P < 0.05$ was considered statistically significant.

Results

Characteristics of the Studied Population

The studied population were divided into 3 groups, non-severe ($n=185$; 37.3%), severe ($n=165$; 33.3%) and, critical ($n=146$; 29.4%); older patients were found in the critical group (median age =61) then the severe group (median age=55) while, the youngest were among the non-severe group (median age =33.5) with a significant difference between them ($p < 0.001$). Most of the patients were males in all groups.

In comparing associated co-morbidities, the critical group was more associated with diabetes mellitus (DM), hypertension (HTN), cardiovascular diseases and, chronic obstructive pulmonary diseases (COPD) versus the non-severe and severe groups ($p < 0.001$).

Regarding hematological parameters, the hemoglobin level was least in the severe group [median (IQR); 12 (10–13)], and highest in the non-severe group [Median (IQR); 12 (11–14) $p = 0.04$]. Surprisingly, platelets were lowest in the non-severe group, with a significant difference between the three groups ($p < 0.001$). TLC, ANC, AMC, NLR, d-NLR and, PLR were highest in the critical group, followed by the severe group and least in the non-severe group with a significant difference ($p < 0.001$ for all except AMC p -value=0.033). ALC and LMR were inversely proportionate to severity ($p = 0.049$ and < 0.001 , respectively).

Higher CRP and d-dimer levels were reported in the critical group ($p < 0.001$). At the same time, higher ferritin was found in the severe group more than the critical and non-severe groups ($p < 0.001$, $p=0.005$ respectively).

The critical group patients had multi-slice computed tomography (MSCT) imaging, which showed more extensive lesions (either bilateral lesions or multiple unilateral

lesions) than in the non-severe and severe groups ($p < 0.001$). We used CORAD system to assess the probability of COVID-19 infection in our studied cohort; most of them were CORAD 6. CORAD 1, 2 were reported in the non-severe group, while only three patients were in the severe group.

In comparing the oxygen supplementation given to the patients, most of the severe group patients (83%) received oxygen aid, and only 10% were mechanically ventilated. In comparison, 92.5% received oxygen aids in the critical group, and 72.4% required mechanical ventilation.

Most of the non-severe group recovered (93%) and discharged home. The death was more in the critical (65.1%) and severe (15.2%) groups. Demographic and baseline data of the studied cohort are shown in (Table 1).

ROC Curve to Detect Optimal Cut-off Values of the Hematological Ratios

We analyzed the optimal cut-off values of NLR, d-NLR, LMR, and PLR calculated by the ROC analysis and presented in (Figure 1). Areas under the curve (AUC) of NLR, d-NLR, PLR and LMR were 0.838, 0.817, 0.643, and 0.285, respectively. LMR could not be used as a potential diagnostic biomarker for subsequent analysis because its AUC was less than 0.50. The optimal cut-off values were NLR (3.5), d-NLR (2.86), and PLR (192). D-NLR had the highest specificity (89.19%), followed by NLR (87%) then PLR (77.62%). The most heightened sensitivity was in favor of NLR (71.38%), then the d-NLR (67.2%), and the PLR (50%; Table 2).

Survival Analysis with Kaplan–Meier Curves

The estimated mean time until death was 21.3 days for non-severe vs 19.1 days for severe vs 16.2 days for critical patients ($p < 0.0001$). The survival probability is lowest in critical patients at all-time points, so they are less likely to survive (Figure 2A).

We estimated the mean survival time according to NLR (estimated mean time until death is 20.5 days for NLR < 3.5 and 17.7 days for NLR > 3.5 ; $p < 0.001$), d-NLR (The estimated mean time until death is 20.2 days for d-NLR < 2.5 and 17.5 days for d-NLR > 2.5 ; $p < 0.001$), and PLR (the estimated mean time until death is 19.3 days for PLR < 192 and 18.8 days for PLR > 192 ; $p=0.04$). So, it is obvious that those patients with NLR > 3.5 , d-NLR > 2.5 , or PLR > 192 are less likely to survive (Figure 2B–D).

Table I Characteristics of the Studied Population

Variant	Group			P-value
	Non-Severe n=185 (37.3%)	Severe n=165 (33.3%)	Critical n=146 (29.4%)	
Age/years	33.5 (26–54)	55(47–62)	61(50–69)	<0.001*
Sex/males n (%)	92 (49.5)	94 (57)	87 (60)	0.167**
Smoking n (%)	41 (22%)	36 (21.8%)	29 (20)	0.867**
Co-morbidities				
• DM n (%)	16 (8.6)	39 (23.6)	42 (29)	<0.001**
• HTN n (%)	19 (10.3)	40 (24.2)	73 (50.3)	<0.001**
• Cardiovascular diseases n (%)	10 (5.4)	31 (18.8)	54 (37)	<0.001**
• COPD n (%)	4 (2.2)	15 (9.1)	20 (13.7)	<0.001***
Laboratory data				
CBC median (range)				
HB (g/dL)	12 (11–14)	12 (10–13)	12 (11–13)	0.043*
Platelets ($\times 10^9/L$)	204 (136–264)	234 (162–325)	231 (167–328)	<0.001*
TLC ($\times 10^9/L$)	4 (3.1–6)	8 (5–12)	11 (9–15)	<0.001*
ANC ($\times 10^9/L$)	2 (1.4–4)	6 (3–9.5)	9 (7–12)	<0.001*
ALC ($\times 10^9/L$)	1.53 (1–2)	1 (1–2)	1 (1–2)	0.049*
AMC ($\times 10^9/L$)	0.2 (0–1)	1 (0–1)	1 (0–1)	0.022*
NLR	1.55 (1–3)	4 (2–8)	8 (5–11)	<0.001*
LMR	4 (3–6)	3 (2–5)	2 (1–3)	<0.001*
d-NLR	1 (1–2)	3 (1–5)	5 (3–7)	<0.001*
PLR	131 (91–188)	172 (103–286)	203 (107–324)	0.001*
Inflammatory markers				
CRP (mg/l)	20 (4.5–54)	54 (30.1–82)	79 (45–85)	<0.001*
Ferritin (mcg/mL)	189 (68–408)	191(98–450)	145 (40.5–202)	0.001
D- dimer (mcg/mL)	0.81 (0.26–9.2)	3 (0.69–17)	8 (1.5–20)	<0.001
MSCT chest				
• Bilateral affection or multiple unilateral affection n (%)	172(93)	164(99.4)	146(100)	<0.001***
Oxygen support				
• Any oxygen aids other than mechanical ventilation n (%)	–	137(83.0)	135(92.5)	<0.001**
• Mechanical ventilation n (%)	–	17(10)	105(72.4)	<0.001**
Outcome				
• Recovery n (%)	172(93)	140(84.8)	51(34.9)	<0.001**
• Death n (%)	13(7)	25(15.2)	95(65.1)	<0.001**

Notes: *Kruskal–Wallis test. **Chi square test. ***Fisher's Exact test. Bold is significant *p* value; *P* value is significant if <0.05.

Abbreviations: ALC, absolute lymphocyte count; AMC, absolute monocyte count; ANC, absolute neutrophil count; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; DM, diabetes mellitus; d-NLR, derived neutrophil to lymphocyte ratio; HB, hemoglobin; HTN, hypertension; LMR, lymphocyte to monocyte ratio; MSCT, multi-slice computed tomography; n, number; NLR, neutrophil to lymphocyte ratio; PLR, platelets to lymphocyte ratio; TLC, total leukocyte count.

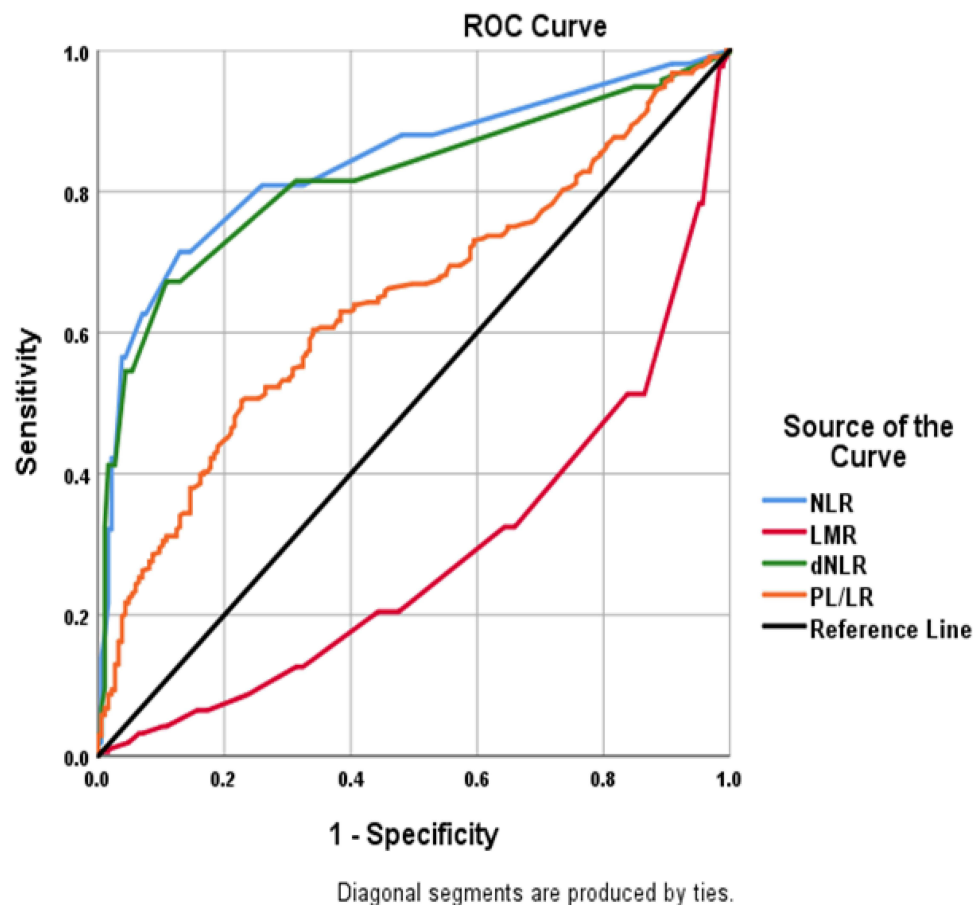


Figure 1 ROC curve was used to study the optimal cut off values of different hematological ratio; NLR (3.5), d-NLR (2.86), and PLR (192). D-NLR specificity (89.19%) NLR (87%) and PL/LR (77.62%). The sensitivity of NLR (71.38%), d-NLR (67.2%) and the PL/LR (50%).

Abbreviations: D-NLR, derived neutrophil lymphocyte ratio; LMR, lymphocyte monocyte ratio; NLR, neutrophil lymphocyte ratio; PLR, platelets lymphocyte ratio.

Identification of Possible Predictors of Severity in COVID-19 Patients

To determine the effect of hematological ratios on the prognosis of COVID-19 patients, we also performed Kaplan–Meier survival analysis and COX regression analysis to explore the possible independent predictors for severe COVID-19. Further univariate and multivariate analysis of

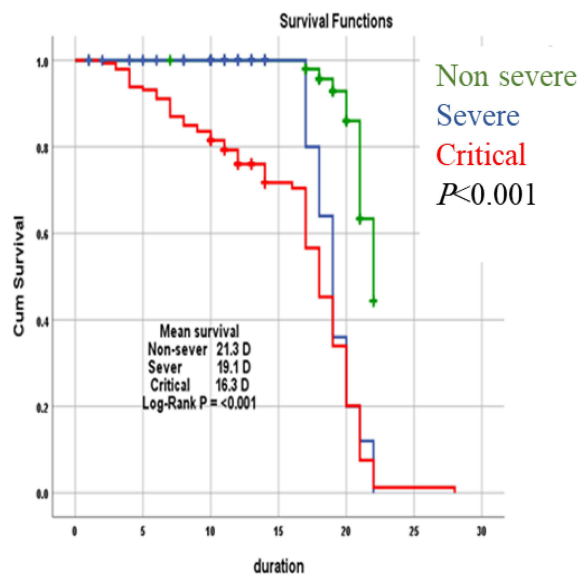
COX regression showed that the estimated NLR (HR 1.056, 95% CI 1.037–1.075), d-NLR (HR 1.075, 95% CI 1.045–1.104), and PLR (HR 1.001, 95% CI 1–1.002) identified by univariate Cox regression but in multivariate Cox regression, only elevated NLR (HR 1.046, 95% CI 1.024–1.069) was the independent adverse factor affecting recovery and discharge of patients with COVID-19.

Table 2 ROC Curve Analysis of All Studied Population to Detect Optimal Cut-off Values, Sensitivity and Specificity of the Hematological Ratios

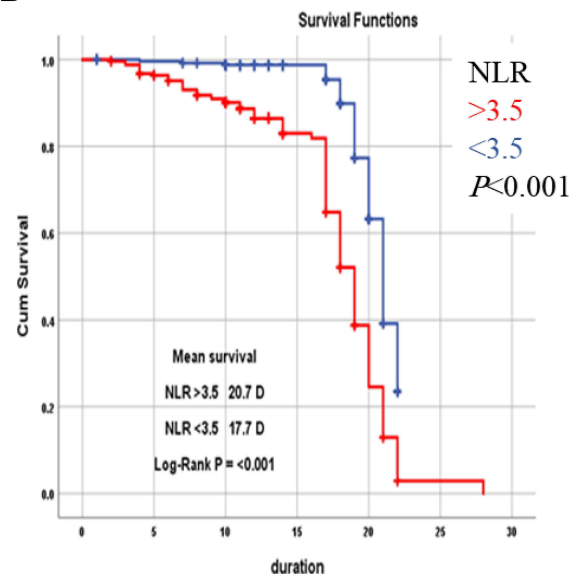
	AUC	P value	95% CI		Cut off Point	Sensitivity	Specificity	+LR	–LR	+PV	–PV	Youden's Index
			Lower	Upper								
NLR	0.838	<0.001	0.803	0.874	>3.5	71.38%	87.03%	5.50	0.33	90.2	64.4	0.5841
d-NLR	0.817	<0.001	0.780	0.854	>2.86	67.20%	89.19%	6.22	0.37	91.3	61.8	0.5639
PLR	0.643	<0.001	0.595	0.692	>192	50.00%	77.62%	2.20	0.65	78.7	48.0	0.2762
LMR	0.285	<0.001	0.239	0.331	≤3	67.64%	65.95%	1.99	0.49	76.8	55.0	0.3395

Notes: The test variable(s): NLR, d-NLR, PLR and LMR has at least one tie between the positive actual state group and the negative actual state group. *P* value is significant if <0.05.

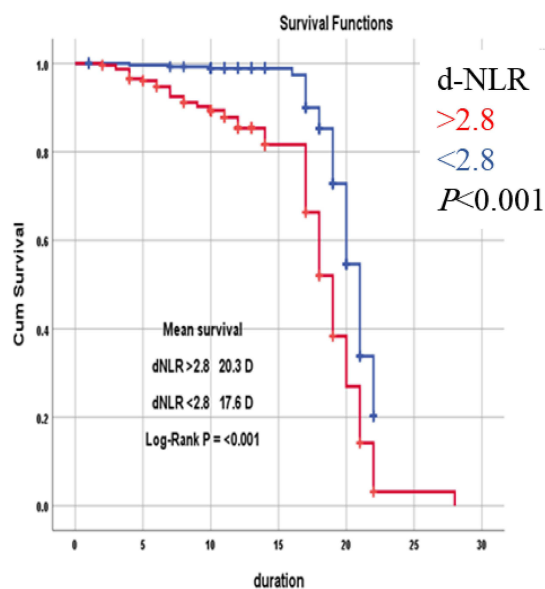
Abbreviations: AUC, area under curve; CI, confidence interval; d-NLR, derived neutrophil lymphocyte ratio; LMR, lymphocyte monocyte ratio; LR, Likelihood ratio; NLR, neutrophil lymphocyte ratio; PLR, platelet lymphocyte ratio; PV, predictive value; ROC, receiver operating characteristics.

A

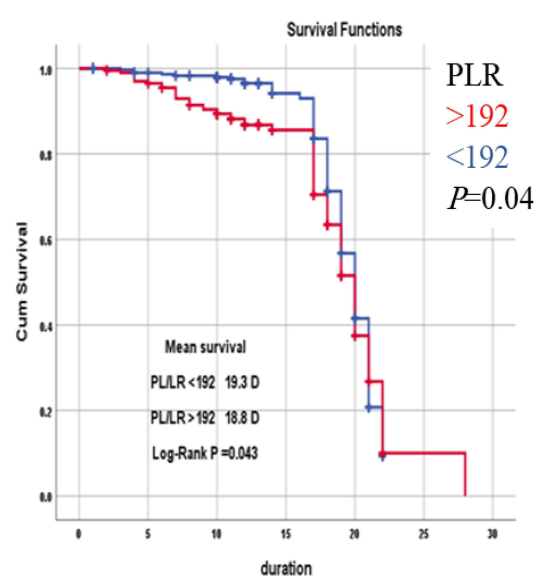
Non-sever	184.5	183.5	116	39	18	0	0
Sever	162	156	89	25	9	0	0
Critical	164	137	96.5	57	27	1	0

B

NLR < 3.5	247	243	150	51	25	0	0
NLR > 3.5	245	233	151	70	29	1	0

C

d-NLR < 2.8	264	260	163	59	28	0	0
d-NLR > 2.8	228	216	138	62	26	1	0

D

PLR < 192	292	284	183.5	75.5	35.5	0	0
PLR > 192	199.5	191.5	117.5	46	19	1	0

Figure 2 Survival analysis using Kaplan–Meier curve (A) Kaplan–Meier curves showing survival in non-severe, severe and critical group. (B) Kaplan–Meier curve according to NLR (Neutrophil lymphocyte ratio) of COVID-19 patients. (C) Kaplan–Meier curve according to d-NLR (derived neutrophil lymphocyte ratio) of COVID-19 patients. (D) Kaplan–Meier curve according to PLR (platelets lymphocyte ratio) of COVID-19 patients. Numbers below each curve show number at risk.

Table 3 Identification of Possible Predictors of Severity in COVID-19 Patients

	Univariable Odds Ratio	95% C. I		P value	Multivariable Odds Ratio	95% C.I		P value
		Lower	Upper			Lower	Upper	
Age	1.069	1.055	1.084	<0.001	1.056	1.009	1.098	0.018
DM (yes/no)	3.698	2.087	6.551	<0.001	1.852	0.790	4.338	0.156
HTN (yes/no)	4.956	2.923	8.404	<0.001	0.823	0.345	1.963	0.661
Cardiovascular diseases (yes/no)	6.582	3.320	13.048	<0.001	1.796	0.618	5.215	0.282
COPD (yes/ no)	5.759	2.013	16.480	0.001	4.058	0.921	17.878	0.064
NLR	1.602	1.450	1.771	<0.001	1.453	1.123	1.765	0.003
d-NLR	1.913	1.654	2.212	<0.001	1.002	0.827	1.204	0.983
PLR	1.004	1.002	1.006	<0.001	1.000	0.998	1.003	0.681
LMR	0.784	0.726	0.847	<0.001	1.020	0.900	1.156	0.757
CRP	1.013	1.008	1.018	<0.001	1.006	1.003	1.009	0.043
Ferritin	1.001	1.000	1.002	0.154				
D- dimer	23.362	12.617	43.259	<0.001	46.957	15.689	140.547	<0.001
Steroid (yes/no)	3.832	1.532	9.583	0.004	1.160	0.315	4.270	0.823
Oxygen aids (yes/no)	40.813	24.061	69.228	<0.001	22.031	11.733	38.621	<0.001
Mechanical (yes/no)	12.452	5.910	26.238	<0.001	1.852	0.736	4.662	0.191

Notes: Bold is significant *p* value; *P* value is significant if <0.05.

Abbreviations: COPD, chronic obstructive pulmonary disease; CI, Confidence interval; CRP, C-reactive protein; DM, diabetes mellitus; d-NLR, derived neutrophil to lymphocyte ratio; HTN, hypertension; LMR, lymphocyte to monocyte ratio; NLR, neutrophil to lymphocyte ratio; PLR, platelets to lymphocyte ratio.

The univariate logistic regression analysis showed age, DM, HTN, cardiovascular diseases, COPD, NLR, d-NLR, LMR, PLR, CRP, d-dimer, steroid, oxygen aids, and mechanical ventilation were associated with increased severity of COVID-19. Subsequently, all the above univariate analysis parameters with statistical significance were integrated for in-depth analysis into the multivariate logistic regression model. In the multivariate logistic regression model, considering the likelihood of overfitting, we assumed a stepwise forward method for logistic regression analysis to decrease the number of independent variables entering the model to reduce the probability of overfitting the model.

The results showed that the early independent predictors for severe COVID-19 were age, NLR, CRP, d-dimer, and oxygen aid upon entry, while the role of d-NLR, LMR, and PLR is unclear (Table 3).

Discussion

A cluster of cases of pneumonia of unknown etiology started to emerge in Wuhan, China, at the end of 2019, a striking event

that terrifies the whole world. A rapid spread of that infection took place with a relatively low mortality rate.³ At the end date of the collection of data (2020-12-5), more than one and a half million deaths were reported to WHO. Mortality rates vary from one region to another; it was less than 2.5% in CDC, China, but in Egypt, the mortality rate was higher, reaching up to 6.7%. Lack of accurate recording and delayed diagnosis may play a significant role in explaining such a high mortality rate. This issue pushed us to investigate possible cheap, rapid, and simple predictors that may force attention to more risky victims.

Not enough data supporting increased liability of COVID-19 infection to patients with chronic diseases but, many previous researchers –in line with our results– confirmed the increased severity in older people, especially those suffering from diabetes mellitus (DM),¹⁵ hypertension (HTN)³ cardiovascular diseases;¹⁶ also, we reported increased severity in chronic obstructive pulmonary disease (COPD) patients which appears logic as the virus affects mainly the respiratory system and it is well known that serious adverse effects are

associated with respiratory viral infections in those with COPD;¹⁷ chronic pulmonary diseases, however, are under-reported, according to the first epidemiological studies and detected only in 0.3–2.5% without a significant increase in risk as it was expected.¹⁸

C-reactive protein (CRP), d-dimer and ferritin, are markers that are extensively studied in COVID-19 infected victims.^{19–21} CRP levels correlate with the degree of inflammation. Interestingly, it was found to increase parallel to the increase in the diameter of the largest pneumonia lesion in COVID-19 patients;¹⁹ this supports our findings in which CRP is least in the non-severe group. D-dimer >2 was found in an early study to be the only factor associated with mortality in COVID-19 patients;²⁰ this is also observed in our results, where it was highest in the critical group. Hyperferritinemia in a large meta-analysis found to be associated with severe conditions and adult respiratory distress syndrome (ARDS).²¹ However, Wu et al found that ferritin was neither associated with ARDS nor severe cases of COVID-19.²² Surprisingly, in ours, mean ferritin levels favored the severe group, not the critical one.

The complete blood count is the test used to approach varieties of infections, with the advantages of being available and highly informative. In the Chinese population, leucopenia was reported in COVID-19 patients at the expense of lymphopenia without investigating its relation to disease severity.²³ In our research, critical group patients suffered from the lowest lymphocyte count and the highest leukocyte count mostly due to neutrophilia, which could be explained by secondary bacterial infection occurred in most critical cases; this was also approved previously by a large meta-analysis;²⁴ Recently, an autopsy report on a 50-year-old COVID-19 patient with ARDS revealed that although the peripheral blood lymphocyte count was dramatically decreased, there was inflammatory lymphocyte infiltration in both lungs and immune hyperactivation.²⁵ Lymphopenia in COVID-19 patients can be explained by varieties of theories, as the ability of the virus to infect lymphocytes,²⁶ to destroy lymphatic organs like the thymus and spleen, to disturb the levels of interleukin (IL)-6 and other inflammatory cytokines may result in lymphocyte apoptosis,²⁷ and the inhibition of lymphocytes proliferation by metabolic molecules as the lactic acid.²⁸ High monocyte count is another hematological parameter found more in critical population, representing the main generators of inflammation in COVID-19 and predisposing to serious outcomes mostly due to “a dysregulation syndrome”;²⁹ in contrary, the

difference in monocyte count between healthy and COVID-19 patients was not significant in another study.³⁰

In the present study, we concentrated on the value of the hematological ratios as NLR, d-NLR, LMR and, PLR; our results supported a previous study that indicated that elevated NLR predicts poor outcome in COVID-19 patients so that those with high NLR attract more attention than those with low NLR.^{6,7,30} It is well established that NLR tends to increase with severe infection or systemic inflammation in line with the magnitude of clinical status and outcome.³¹ NLR, as well as, age were independent factors for poor clinical outcome of COVID-19 in Chinese cohort. NLR was one of the earliest studied markers that were correlated with severity.^{4,32,33} The following are potential explanations for these findings in COVID-19 patients; on the one hand, neutrophil releases large amounts of reactive oxygen species stimulates the antibody-dependent cell-mediated cell (ADCC) that can directly kill the virus, expose virus antigen, and activate cell-specific and humoral immunities.³⁴ Besides, neutrophil produces numerous cytokines, such as circulating vascular endothelial growth factor (VEGF), which is profoundly expressed in COVID-19 patients.³⁵ Moreover, several inflammatory factors, including interleukin-6, tumor necrosis factor-alpha, granulocyte colony-stimulating factor, and interferon-gamma factor, can trigger neutrophils.^{36–38} On the other hand, viral infections mostly affect lymphocytes,³⁹ as systematic inflammation causes marked suppression of CD4+ T lymphocytes and increases CD8+ suppressor T lymphocyte.⁴⁰ Thus, the critical group had higher NLR in comparison to severe and non-severe groups.

We studied a unique ratio derived from the NLR and named the d-NLR; this ratio was previously correlated with severity in chronic and neoplastic conditions.⁴¹ According to our knowledge, few studies had investigated its role in Covid-19 cases.⁴ Surprisingly, d-NLR carried the highest specificity among all studied factors with an optimal cut-off value of 2.86.

Another attractive ratio is LMR, which was signed in its lower values in critical patients of COVID-19. This finding was previously detected but concerning community-acquired pneumonia without identification of the causative pathogen.^{32,42,43} In another study, 190 COVID-19 patients were enrolled, and LMR was significantly lower than the healthy group, with a significant negative correlation with body temperature.³⁰

PLR is a new inflammatory index of interest, which is more valuable than the simple platelet or lymphocyte count. It mostly reflects changes in platelets, which are

considered to have a unique role in inflammation and immune response,^{32,44} and higher in the critical group in our study. Previous investigators proved that peak PLR is more elevated in severe populations than in non-severe.⁴⁵ In addition to a significant correlation with a poor prognosis on COVID-19,⁴⁵ while others failed to detect any value to such index in COVID-19 patients.⁴⁶

The optimal thresholds for NLR, d-NLR, PLR, and LMR were estimated using the ROC curve. The NLR yielded the highest AUC value than the other ratios, and its optimal cut-off value was 3.5, with 87.03% specificity and 71.38% sensitivity. In line with ours, a previous study showed that NLR had the highest AUC value with a relative cut-off value (3.3) with the highest specificity and sensitivity (63.6% and 88%, respectively).⁴ In a comparable study, the monocyte to lymphocyte ratio (MLR) had the highest AUC value with an optimal cut-off value of 0.23, with 90.00% specificity and 75.79% sensitivity (9). Some studies have shown that a surrogate predictor for influenza A is an LMR value <2.⁴⁷

To predict severity in COVID-19 patients, regression analysis found that age, NLR, CRP, d-dimer, and oxygen aid on admission were reasonable predictors. In agreement with ours, previous research confirmed the prediction role of NLR in COVID-19 patients.⁴ Another one found that PLR value was an independent determining factor in severe patients.⁴⁵

There are some limitations to this study. First, the research was retrospective. The data were recruited from hospital medical records after a set of criteria were met, which carry the risk of selection bias. Second, because of data limitation, we only used one measure in time rather than a longitudinal measure. Third, despite trials to exclude confounding factors, some confounders might affect the value of the hematological ratios.

In conclusion, NLR is a predictor for severity in COVID-19. LMR, d-NLR, and PLR may assist in risk stratification. According to our observations in this study, NLR can improve risk stratification of COVID-19 severity, LMR, d-NLR, and PLR can be quick, cost-effective, and interesting potential markers.

Ethical Approval

Authorization of the local research ethics committee of Assiut University.

Consent to Participate

Authors consented to participate in this research article.

Encrypted patients' data was collected from hospital reports without a written consent; the reason for the written consent waiver was that the research presents no risk of harm to participants and involves no procedure for which written consent is normally required outside of the research context (retrospective survey) as well as participant verbally approved documentation and reporting of their medical and laboratory information. Approval of the local research ethics committee (IRB number: 17300513) according to the Declaration of Helsinki was provided. Patient data confidentiality was maintained.

Consent for Publication

Authors consented for publication.

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.

Disclosure

The authors declare no conflicts of interest in this work.

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