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Evaluation the Prognostic Value of Peripheral Blood Counts in Covid-19 Patients

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ABSTRACT

Background: The outbreak of novel Coronavirus Disease-2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a major pandemic situation and a catastrophe for humans. COVID-19 is a severe infectious disease particularly of the respiratory system characterized by fatal complications. In fact, the current crisis of COVID-19 has become an increasingly serious concern to public health. Since there are no specific drugs and/or vaccines available so far and continues gene mutations. COVID-19 patients showed several abnormal hematological findings. Including lymphopenia, neutrophilia, elevated levels of D-dimer and fibrinogen. COVID-19 remains to be a major challenge task. **Objective:** Our study was conducted to evaluate the prognostic value of peripheral blood counts in Covid- 19 patients. **Patients and methods:** Our study was a Prospective cohort study. It was conducted on 100 patients with Covid -19 at and post admission **Results:** there was positive correlation between NLR and PLR with C- reactive protein (CRP), LDH, ferritin, Procalcitonin, IL 6 and D-dimer along course of the disease. However, LMR was found to be negatively correlated with them. It was found that if NLR and PLR increased there would be an increase in severity of the disease as long as the risk of ICU admission and intubation. **Conclusion:** Our study revealed that, NLR and PLR in addition to LMR are good prognostic factors in COVID 19 patients that are cost-effective, readily available, and easy to calculate and can be used instead of other inflammatory markers e.g. (CRP, IL6, D-dimer, ferritin and procalcitonin).

Keywords: Corona virus, severe acute respiratory distress syndrome, cytokine release syndrome

1. Introduction

The new COV causes disease named as severe acute respiratory syndrome (SARS)-CoV-2 and coronavirus disease 2019 (COVID-19) which emerges as global health threat (Fisher and Heymann 2020). Although covid-19 is a primary respiratory disease it can affect multiple systems (Driggin *et al.,* 2020).

Hematological parameters, as peripheral blood counts and coagulation tests, have become prominent in predicting the severity of the COVID-19 from the outset (Tang *et al.,* 2020). The neutrophil to lymphocyte ratio (NLR) was found to have a prognostic value in several cases including sepsis, cardiovascular diseases, and malignant tumors, etc. (Russell *et al.,* 2019).

The majority of Covid -19 severe cases present low counts of lymphocytes, monocytes, eosinophils and basophils and higher counts of leucocytes (Qin *et al.,* 2020). NLR is found to be an easy, available, cost-effective and reliable parameter, which on continuous monitoring could be effective for the diagnosis and treatment of COVID-19 (Jimeno *et al.,* 2021).

Covid19 critical status is associated with high mortality rate which is linked to SARS-CoV-2 infection-induced hyperinflammation of the innate and adaptive immune systems which results in cytokine storm, a cytokine release syndrome (CRS)-like syndrome in severe/critical COVID-19 cases (Cummings *et al.,* 2020).

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The aim of this work was to evaluate the prognostic value of peripheral blood counts in Covid-19 patients.

2. Patients and Methods

Our study is a Prospective cohort study at which patients' data were observed and collected throughout the time of our study. It was conducted on 100 patients with Covid -19 at and post admission taking duration of Six months from May 2021 to October 2021. The following are the inclusion and exclusion criteria of our study:

Inclusion Criteria: Patients aged > 18 years old. Patients with respiratory symptoms (cough, dyspnea, fever). Patients hospitalized to intensive care unit in case of respiratory distress syndrome.

Exclusion criteria: Patient unwilling to participate into the study. Other hematological disorders. Other infection other than covid-19. Pregnant females.

Provision of privacy*:* Privacy of all data was guaranteed as the following: There was a code number for each patient, so the data of patients were strictly confidential.

Possible Hazards during the research:

High risks of getting infection during contact with suspected or infected patient, it was avoided by highly protective personal equipment and using major sterile and disinfectant techniques. No other hazards are expected during the period of research. There was safe disposal of waste products e.g., needles…etc. Any unexpected risks that appeared during the course of the research were cleared to participants and the ethical committee on time.

All the participants will be subjected to:

Consent: Permission was obtained from Research Ethics Committee as a part of the Quality Assurance Unit in the Faculty of Medicine at Tanta University to conduct this study and to use the facilities in the hospital. Informed written consent was obtained from all patients after a full explanation of the benefits and risks.

History taking: age, gender, onset, course, and cause of the disease.

Complete clinical examination

Assessment of vital signs of the patient including blood pressure, O_2 saturation, pulse, temperature, random blood glucose, chest auscultation & abdominal and cardiac system examination.

Laboratory investigation

Blood samples collected on EDTA tubes for complete blood count (CBC). Serum samples for assayed for serum ferritin, lactate dehydrogenase (LDH), liver function tests (alanine aminotransferase (ALT), aspartate aminotransferase (AST), procalcitonin, renal function (blood urea and serum creatinine), C-reactive protein (CRP) and interleukin – 6 (IL-6). Citrated blood samples for coagulation profile (partial thromboplastin time (PTT), prothrombin time (PT) and D-dimer.

Imaging procedures

High resonance computerized tomography (HRCT) without contrast.

Statistical analysis

Data were analyzed using the IBM® SPSS statistical soft-ware, version 21. We used the one-sample Kolmogorov-Smirnov test to check the normality of data and the data were non-parametric. Numerical data was presented as mean and standard deviation (SD) and categorical data was presented as number and percentage. Chi-squared test was used for comparing the qualitative data. Wilcoxon test was used to compare between two means in the same group at and after the admission. Also, while Kruskal Wallis test was used to compare the two means in different groups. Linear correlation analysis was done by spearman coefficient correlation and used for test the positive or

negative associations between different variables. For the risk estimated, Linear regression was used to detect the predictor variables. The level of significant was adopted at $p<0.05$.

3. Results

Table shows that males are more affected than females and There is positive correlation between prognosis and age. The increase the age, the increases mortality rate (Table 1)

Table 1: Demographic data of different studied groups:

Demographic data	Cases (n = 100)	
	No.	%
Age		
Min - Max	31 – 85	
Mean + SD	52.22 + 21.45	
Gender		
Male	61	61.0%
Female	39	39.0%

On following up, NLR and PLR values showed statistically insignificant increase after admission to a maximum of 239.24 and 2450.3 respectively indicating bad prognosis. On the other hand, LMR decreased statistically insignificant from 14.61 down to 0.11 correlating to bad prognosis and high mortality rate (Table 2).

Table 2: Ratio at admission and after admission among the studied patients:

		At admission (n = 100)	After admission (n = 100)	W- Test (p value)
NLR	Min.–Max	1.42 – 53.74	0.79 – 239.24	**0.19 (0.88)**
	Mean ± SD.	11.48 + 9.06	18.25 + 31.22	
	Median	8.14	6.94	
PLR	Min.–Max	53.36 – 1290.0	46.38 – 2450.3	**1.18 (0.23)**
	Mean ± SD.	332.25 + 195.27	349.36 + 336.36	
	Median	278.5	252.45	
LMR	Min.–Max	0.52 – 14.61	0.11 – 12.58	**0.53(0.59)**
	Mean ± SD.	3.28 + 2.55	4.83 + 3.14	
	Median	2.07	2.02	

W: Wilcoxon Signed Ranks Test. *: Statistically significant at $P \leq 0.05$

The table shows the relation between inflammatory markers and disease severity and death where HB, platelet and monocytes were found to be statistically insignificant in predicting disease severity and mortality rate. On the other hand, some inflammatory markers were found to be statistically significant in predicting disease severity such as: WBCs, Lymphocytes, Neutrophils NLR, PLR, LMR, CRP, LDH, Serum ferritin, IL 6, D-Dimer and Procalcitonin for which p value was estimated to be less than 0.05. In addition, most importantly O2 saturation also was found to be a very important predicting factor of disease severity with statistically significant as p value <0.05 (0.03). (Table 3)

According to the table, there are negative correlation between prognosis and O2 saturation, platelets, Hb, LMR and lymphocytic count. (the less those values the more severe the disease). On the other hand, there are positive correlation between prognosis and the other inflammatory markers listed in the proceeding table where the more these values the more severe the disease including: LDH, IL6, D-dimer, NLR, PLR, Ferritin, CRP, Procalcitonin. In addition to the above, we found that age has positive correlation with prognosis and mortality rate. Statistical significance was found in all markers either with positive or negative correlation with P value <0.05 except Monocyte P value 0.45 (Table 4).

This table shows a comparison between inflammatory markers correlated with NLR, PLR, LMR after admission. serum ferritin, LDH, IL6, D-Dimer and CRP were positively correlated with statistical significance with P value < 0.05 except procalcitonin with P value 0.12. LDH and IL6, serum ferritin and CRP were statistically significant with PLR whereas, only LDH positively

correlates with LMR with statistical significance. Consequently, NLR, PLR, LMR are good prognostic markers in Covid 19 and can be used instead (Table 5).

Analysis of our collected data revealed that mean duration of hospital stay before death was 5 weeks or more for 50% of died patient. While only 25% of cases survived for 6 weeks or more. Median of duration for all died patients was estimated to be 4 weeks (Table 6).

Table 3: Relation between inflammatory markers and the prognosis among the studied patients:

	Live (n = 68)	Death (n = 32)	K- Test (p value)
O_2 saturation	90.09 + 6.20	74.10 +10.23	**9.01 (0.03) ***
Hgb	12.41 + 1.81	11.99 + 2.48	**0.37 (0.54)**
WBCs	8155.32 + 3521.2	16750.32 + 7743.45	**33.7 (0.001) ***
Platelets	255852.7 + 91452.2	229324.4 + 89324.10	**2.35 (0.14)**
Lymphocytes	1366.55 + 659.21	534.37 + 473.17	**48.4 (0.001) ***
Neutrophils	6279.14 + 3254.23	14965.12 + 7959.21	**30.7 (0.001) ***
Monocytes	431.35 + 199.95	530.78+ 338.67	**1.9 (0.16)**
NLR	5.85 + 4.40	44.20 + 43.25	**46.8 (0.001) ***
PLR	227.64 + 145.00	608.77 + 262.32	**35.2 (0.001) ***
LMR	6.01 + 1.25	2.33 + 5.41	**36.0 (0.001) ***
CRP	31.11 + 46.02	281.25 + 224.21	**50.8 (0.001) ***
Serum ferritin	251.12 + 304.25	1823.70 + 1110.24	**46.2 (0.001) ***
IL 6	7.76 + 16.66	248.44 + 427.79	**57.3 (0.001) ***
LDH	270.53 + 154.88	480.53 + 499.88	**53.3 (0.001) ***
D-Dimer	0.51 + 0.90	9.16 + 16.62	**45.7 (0.001) ***
Procalcitonin	0.08 + 0.27	10.09 + 15.25	**46.0 (0.001) ***

K: Kruskal Wallis Test *: Statistically significant at $P \leq 0.05$

Table 4: Spearman correlation between prognosis and inflammatory markers among studied patients:

Cases	Prognosis	
	r	P-value
Age	0.56	0.001*
O_2 saturation	-0.71	0.003*
Hb	-0.42	0.02*
WBCs	0.22	0.02*
Platelets	- 0.21	0.03*
Lymphocytes	- 0.35	0.001*
Neutrophils	0.51	0.001*
Monocytes	0.07	0.45
NLR	0.67	0.001*
PLR	0.53	0.001*
LMR	- 0.55	0.001*
CRP	0.64	0.005*
Serum ferritin	0.64	0.001*
LDH	0.58	0.001*
IL 6	0.60	0.002*
D-Dimer	0.65	0.001*
Procalcitonin	0.63	0.001*
CT	0.76	0.001*

Table 5: Spearman correlation between NLR, PLR, LMR and other inflammatory markers after admission among studied patients.

Cases	NLR		PLR		LMR	
	R	P-value	r	P-value	R	P-value
Serum ferritin	0.64	0.001*	0.43	0.002*	-0.03	0.11
LDH	0.31	0.001*	0.16	0.001*	0.19	0.04*
CRP	0.57	0.001*	0.43	0.02*	-0.10	0.30
IL 6	0.84	0.002*	0.19	0.05*	-0.15	0.41
D-Dimer	0.31	0.001*	0.16	0.51	-0.06	0.51
Procalcitonin	0.17	0.12	0.15	0.32	-0.09	0.16

Table 6: Means, Medians and percentile for Survival Time (weeks) of cases died by Covid- 19:

Mean				Median			
		95% Confidence Interval				95% Confidence Interval	
Estimate	Std. Error	Lower Bound	Upper Bound	Estimate	Std. Error	Lower Bound	Upper Bound
4.781	0.338	4.118	5.444	5.000	0.427	4.162	5.838
25.0%		50.0%		75.0%			
Estimate	Std. Error	Estimate	Std. Error	Estimate	Std. Error		
6.000	0.257	5.000	0.427	4.000	0.314		

4. Discussion

COVID-19 is a systemic multiorgan disease caused by SARS-CoV-2 with the lung as the primary target organ resulting in severe acute respiratory syndrome. Death can occur in severe cases due to acute respiratory distress syndrome (Guan *et al.,* 2020).

Patients with COVID-19 typically have higher inflammatory cytokine levels including; IL-6 and TNF-α compared with healthy individuals (Del Valle *et al.,* 2020). Furthermore, patients with COVID-19 have elevated levels of serologic inflammatory markers such as C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), lactate dehydrogenase (LDH), and procalcitonin (Ali, 2020). These inflammatory cytokines may also alter the levels of various blood cell lineages with most prominently lymphopenia (Tavakolpour *et al.,* 2020).

In recent studies, the neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR), lymphocyte/ monocyte ratio (LMR) which are novel inflammatory markers, have been considered as useful indicators for diagnosis and prognosis of various infectious diseases, including COVID-19 infection (Cunha *et al.,* 2016).

In our study, we evaluate useful diagnostic biomarkers by investigating and comparing the prognostic effects of NLR, LMR, PLR, and C reactive protein ratio (CRP), LDH, ferritin, Procalcitonin, IL 6 and D-dimer in COVID-19 cases.

Our study was a Prospective cohort study that was done between May 2021 to October 2021 on 100 Covid-19 patients following them along the course of the disease.

It was found positive correlation between NLR and PLR with C- reactive protein (CRP), LDH, ferritin, Procalcitonin, IL 6 and D-dimer along course of the disease. However, LMR was found to be negatively correlated with them.

Our study revealed that, NLR and PLR in addition to LMR are good prognostic factors in COVID 19 patients that are cost-effective, readily available, and easy to calculate.

It was found that if NLR and PLR increased there would be an increase in severity of the disease as long as the risk of ICU admission and intubation.

Shang *et al.* (2020) also found a positive correlation between both markers and the duration of hospital stay. As a result, they stated that NLR and PLR could be used to predict severity of patient prognosis (Ding *et al.,* 2020).

Also, Yang *et al.* (2020) found that the ratio of NLR and PLR was higher in severe patients.

Erdogan *et al. (*2021) NLR and PLR values were significantly higher in severe COVID 19 positive patients, supporting the fact that it can be a prognostic biomarker.

Sun *et al.* 2020 and Ding *et al.,* 2020) examined some hematological indices in COVID-19 patients and found that NLR and PLR were significantly higher in severe patients than in non-severe patients. In addition, NLR positively correlated with the duration of hospital stay and has a role in predicting the prognosis of COVID-19 patients.

Damar Çakırca *et al.* (2021) reported that elevated NLR and PLR in non-survivors than survivors and the magnitude of rising was correlated with severity of illness (Luo *et al.,* (2020).

In our study LMR was found to have a negative correlation with severity of the disease; the higher the ratio, the less the severity of disease. Also, Koval *et al.* (2021) revealed the same results indicating that LMR levels on admission negatively correlate with COVID-19 disease severity.

However, Rizo-Téllez *et al.* (2020) found that LMR might have limited benefits in prognosticating COVID-19, as its use as predictor seem to be lower than NLR and PLR, especially in predicting disease severity, ICU admission, and mortality.

Prabhu *et al.,* (2020) reported that LMR was significantly low among severe COVID 19 patients. In addition, Lissoni *et al.,* (2020) and Zhang *et al.,* (2020) found the same results.

While, Yang *et al.* (2020) disagrees with our results reporting that LMR was estimated to be significantly higher in severe cases than less severe ones.

In our study, lymphopenia was found to have a significant correlation with disease severity in agreement with Tavakolpour *et al.* (2020); Erdogan *et al.* (2021) and Muller *et al.* (2021).

Xu *et al.* (2020) found that mononuclear cells, mostly lymphocytes, are dominant in the interstitial tissue of the lung. This explains the reason for the significant decrease in lymphocyte count.

Similarly, Relative lymphocytosis has been found to be characteristic of favorable prognosis according to Tan Li *et al. (*2020).

There was positive correlation between thrombocytopenia and severity of the disease which is also proved by plenty of studies conducted in covid19 patients including (Rohlfing *et al.,* 2021; and Yang *et al.,* 2020).

In addition, according to Mei *et al.,* (2020) thrombocytopenia is associated with critical COVID-19 and increased mortality.

Also, Bomhof *et al.* (2020) reported that Thrombocytopenia is a risk factor for increased morbidity and mortality in SARS-CoV-2 infection (COVID-19 infection). To add, Thrombocytopenia in COVID-19 could be caused by disseminated intravascular coagulation (DIC), sepsis or drug-induced.

According to our study, CRP, procalcitonin and IL6 are inflammatory markers used in prognosis of covid19 in addition to the proceeding ratios and inflammatory mediators.

Xu *et al.* (2020) also reported that the serum levels of Procalcitonin and CRP had prognostic values for COVID-19 mortality with higher sensitivity.

Potere *et al*. (2021) also found that IL-6 is thought to drive multi-organ injury which is the most severe form of the illness.

In addition, IL-6 is involved in the progression of Covid -19 indicating severity patients according to Shekhawat *et al.* (2020).

Overall, on comparison between NLR, PLR and LMR and inflammatory markers including CRP, Procalcitonin and IL6 which are used in prognosis of covid19 severity was found that NLR, PLR and LMR are more reliable than others due to their cost effectiveness, availability and easy to calculate. In addition, they give the same results which also proved by Eissa *et al.* (2021) and Aly *et al.* (2021).

So, there are cheap prognostic markers can be used with the same efficacy of procalcitonin and IL 6 such as NLR, PLR, LMR and platelet count.

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