Original Article

Study of hematological parameters in patients with coronavirus disease 2019 in Basra

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Abstract:

BACKGROUND: Coronavirus disease 2019 (COVID-19) is a novel infectious disease that is caused by SARS-CoV-2, a newly emergent coronavirus, was first recognized in Wuhan, China, in December 2019. Genetic sequencing of the virus suggests that it is a betacoronavirus closely linked to the SARS virus. COVID-19 disease associated with hematological parameter changes like changes in complete blood picture and coagulopathy. Numerous observational studies have suggested that the neutrophil-to-lymphocyte ratio (NLR) and lymphocyte proportion and the platelet-to-lymphocyte ratio (PLR) are inflammatory markers.

OBJECTIVES: The aim was to study the changes in hematological parameters in patients with COVID-19 in relation to the severity and outcome of the disease.

PATIENTS AND METHODS: A prospective study had been done during the period of 3 months that extends from March to May 2020. From 543 patients admitted to the Basra Teaching Hospital COVID-19 wards, 112 medical reports of patients had been randomly selected. The demographic and blood test results for each patient were collected and followed the patient disease severity and the outcome. None of the selected patients had chronic disease or chronic use of medicine (s) that might affect the blood indices. Further analysis and statistics were done by SPSS software.

RESULTS: The study showed that females were more than males 56.25% and 43.75%n respectively. Severity categorization showed that majority of cases were mild (88, 78.58%). Furthermore, the study reveals that 11 (9.82%) had leukocytosis, 6 (5.4%) of patients with leukopenia, 6 (5.36%) of patients with lymphopenia, and 16 (14.28%) of patients with neutrophilia. Seven patients (6.25%) had thrombocytosis while 6 patients (5.36%) presented with thrombocytopenia. Neutrophil/lymphocyte ratio in this study showed 28/112 (25%) patients with N/L ratio ≥3.1. Of those patients with high N/L, 39.29% were aged ≥65 years. All the patients with severe disease had high N/L ($P = 0.000$). The study showed that PLR ≥ 626 was found in 13.39% (15/112) of the studied patients, all of them had either severe (73.3%) or moderate (26.67%) disease which was highly significant when compared to low ratio ($P=0.000$).

CONCLUSION: The study showed that the severity of COVID19 was associated with lymphopenia, monocytosis, and elevated NLR and PLR values. On the other hand, both values (NLR and PLR) could be used as hematological predictors for disease severity and the outcome of patients with COVID-19.

Keywords:

Coronavirus disease 2019, hematological parameters, basrah, leukocytosis, lymphopenia, neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio

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Background

Coronaviruses are important human and animal pathogens. At the end of 2019, a novel coronavirus was identified as the cause of a cluster of pneumonia cases in Wuhan, a city in the Hubei Province of China. It rapidly spreads, resulting in an epidemic throughout China, followed by an increasing number of cases in other countries throughout the world. In February 2020, the World Health Organization (WHO) designated the disease COVID-19, which stands for coronavirus disease 2019.[1]

Most patients with the novel corona virus infection were asymptomatic, yet patients with mild or moderate illness experienced dyspnea 1 week after contact. Severe ill patients progressed rapidly to acute respiratory failure, acute respiratory distress syndrome, metabolic acidosis, coagulopathy, and septic shock. Early identification of risk factors for severe illness facilitated appropriate supportive care and promptly access to the intensive care unit (ICU) if necessary. For mild patients, general isolation and symptomatic treatment were available,

and ICU care was needed unless the condition worsens rapidly, such to reduce the mortality and alleviate the shortage of medical resources. The incubation period for COVID-19 is thought to be within 14 days following exposure, with most cases occurring approximately 4 to 5 days after exposure.[2]

Although the virus that causes COVID-19 is designated severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the patients with severe COVID-19 infection can develop a coagulopathy meeting criteria for disseminated intravascular coagulation per international society of thrombosis and hemostasis criteria, with fulminant activation of coagulation, resulting in widespread microvascular thrombosis and consumption of coagulation factors. This is reflected by thrombocytopenia, prolongation of the prothrombin time/international normalized ratio, partial thromboplastin time, elevation of D-dimer, and decreased fibrinogen levels. Microangiopathy with schistocytes may be observed on the peripheral smear.[3] On the other hand, Most of the severe cases demonstrated elevated levels of infection-related biomarkers and inflammatory cytokines such as serum ferritin and C-reactive protein.[4]

Blood cell interactions are essential in the pathophysiology of inflammation, immune responses, hemostasis, and oncogenesis. Numerous observational studies have suggested that the neutrophil-to-lymphocyte ratio (NLR), lymphocyte proportion, and the platelet-to-lymphocyte ratio (PLR) are inflammatory markers of immune-mediated, metabolic, prothrombotic, neoplastic diseases, and are widely investigated as useful predictors for prognosis in many diseases.[5-7] Recent researches of COVID-19 indicated that severe patients tended to have higher NLR. PLR of COVID-19 between severe (severe and critical) and nonsevere (asymptomatic, mild, and moderate) cases was not fully reported, which may have prognostic values and influence duration of hospitalization and be important therapeutic targets.[4,8]

Finally, some viral infections such as Norwalk virus and hepatitis B virus have clear blood group susceptibility.[9] Recent studies also revealed that people with blood Group A have a higher risk, whereas people with blood Group O have a lower risk for SARS-Cov-2 infection and COVID-19 severity. The distribution of ABO blood groups varies among different races, colors, countries, continents, and other geographical distributions of populations on the planet.[9]

Because of the paucity of local and regional data, the current work was conducted to extend to some extent knowledge about the relation of hematologic parameters

Table 1: Demographic characteristics of patients with coronavirus disease-19

Variable	*n*=112, *n* (%)	Mean±SD
Age (years)		
<15	14 (12.50)	38.31±19.79
15-45	56 (50.00)	
46-65	30 (26.79)	
>65	12 (10.71)	
Gender		
Male	49 (43.75)	
Female	63 (56.25)	
Residency		
Central	54 (48.21)	
Rural	58 (51.79)	
Place of admission		
Ward	105 (93.75)	
ICU	7 (6.25)	
Categories of disease		
Mild	88 (78.58)	
Moderate	13 (11.60)	
Severe	11 (9.82)	
Therapy		
+Plasma therapy	9 (8.04)	
Nonplasma therapy	103 (91.96)	
ABO group		
O group	53 (47.32)	
Non-O group	59 (52.68)	
Length of hospitalization (days)		
≤14	51 (45.54)	17.33±5.70
>14	61 (54.46)	
Outcome		
Improved	107 (95.54)	
Died	5 (4.46)	

ICU: Intensive care unit, SD: Standard deviation

Table 2: The frequencies of hematological parameters in patients with coronavirus disease-19 in relation to degree of severity

Variable	Total number (%)	Degree of severity			P
		Mild *n* (%)	Moderate *n* (%)	Severe *n* (%)	
Hb					
Normal	70 (62.5)	70 (62.5)	0 (0)	0 (0)	0.000*
Anemia	42 (37.5)	18 (16.07)	13 (11.61)	11 (9.82)	
MCV					
Normocytic	87 (77.68)	87 (77.68)	0 (0)	0 (0)	0.000*
microcytic	25 (22.32)	1 (0.90)	13 (11.60)	11 (9.82)	
WBC					
Normal	95 (84.82)	87 (77.68)	8 (7.14)	0 (0)	0.000
Leukocytosis	11 (9.82)	0 (0)	5 (4.46)	6 (5.36)	
Leukopenia	6 (5.36)	0 (0)	0 (0)	6 (5.36)	
ANC					
Normal	94 (83.93)	87 (77.68)	7 (6.25)	(0)	0.000*
Neutrophilia	16 (14.28)	0 (0)	5 (4.46)	11 (9.82)	
Neutropenia	2 (1.79)	0 (0)	2 (1.79)	0 (0)	
ALC					
Normal	102 (91.07)	87 (77.68)	13 (11.60)	2 (1.79)	0.000*
Lymphopenia	6 (5.36)	0 (0)	0 (0)	6 (5.36)	
Lymphocytosis	4 (3.57)	0 (0)	0 (0)	4 (3.57)	
Monocyte					
Normal	86 (76.79)	86 (76.79)	0 (0)	0 (0)	0.000*
Monocytosis	26 (23.21)	2 (1.79)	13 (11.60)	11 (9.82)	
Platelets					
Normal	99 (88.39)	75 (66.97)	13 (11.60)	11 (9.82)	0.741*
Thrombocytosis	7 (6.25)	7 (6.25)	0 (0)	0 (0)	
Thrombocytopenia	6 (5.36)	6 (5.36)	0 (0)	0 (0)	
Ferritin					
Normal	66 (58.93)	66 (58.93)	0 (0)	0 (0)	0.000*
High	32 (28.57)	8 (7.15)	13 (11.60)	11 (9.82)	
Low	14 (12.50)	14 (12.50)	0 (0)	0 (0)	
ESR					
Normal	76 (67.86)	76 (67.86)	0 (0)	0 (0)	0.000*
High	36 (32.14)	12 (10.72)	13 (11.60)	11 (9.82)	

*P value ≤ 0.05 P assessed by Fisher's exact test. WBC: White blood cells, ANC: Absolute neutrophil count, ALC: Absolute lymphocyte count, ESR: Erythrocyte sedimentation rate, MCV: Mean corpuscular volume

Table 3: The degree of severity in patients with coronavirus disease-19 in relation to N\L ratio

Variable	N\L ratio (%)		Total (%)	P
	≥3.1	<3.1		
Disease severity				
Mild	4 (14.28)	84 (100)	88 (78.58)	0.000
Moderate	13 (46.43)	0 (0)	13 (11.60)	
Severe	11 (39.29)	0 (0)	11 (9.82)	
Total	28 (25)	84 (75)	112 (100)	

P assessed by Fisher's exact test. N\L: Neutrophil/lymphocyte

with COVID-19 disease among the local population and to find if any predictive hematologic index.

Methods

The study, prospective observational, was approved by the Ethical and Scientific Committee of Health Directorate and conducted over a 3-month period; March to May 2020 at Basra Teaching Hospital. All Patient gave their written informed consent prior to participation in this study.

Data source and patients

From 543 patients admitted to the Basra Teaching Hospital COVID-19 wards, 112 medical reports of patients had been randomly selected. None of the selected patients had chronic disease or chronic use of medicine (s) that might affect the blood indices. All the patients of any age and gender were diagnosed as cases of COVID-19 depending on the WHO revised criteria for having polymerase chain reaction positive results for either nasal or posterior pharyngeal space.[1]

Variables and outcomes

Demographic and basic hematologic parameters of all enrolled patients were collected alongside with any history of comorbidity and or chronic drug use. The severity of disease is categorized by an expert pulmonologist and according to the WHO classification[10] as mild, moderate, and severe. Admission to the ICU was

Table 4: The degree of severity in patients in relation to neutrophil/lymphocyte ratio (≥3.1) according to age distribution

Variable	N/L (≥3.1) (%)		Total (%)	P
	≥65 years old	<65 years old		
Disease severity				
Mild	0 (0)	4 (23.53)	4 (14.28)	0.000
Moderate	0 (0)	13 (76.47)	13 (46.43)	
Severe	11 (100)	0 (0)	11 (39.29)	
Total	11 (39.29)	17 (60.71)	28 (100s)	

P assessed by Fisher's exact test. N\L: Neutrophil/lymphocyte

Table 5: The degree of severity in patients with coronavirus disease-19 in relation to the blood group

Variables	Blood group (%)		Total (%)	P
	O Group	Non-O group		
Severity				
Mild	51 (96.23)	37 (62.71)	88 (78.58)	0.000
Moderate	0 (0)	13 (22.03)	13 (11.60)	
Severe	2 (3.77)	9 (15.26)	11 (9.82)	
Total	53 (47.32)	59 (52.68)	112 (100)	

P assessed by Fisher's exact test

Table 6: The degree of severity in patients with coronavirus disease-19 in relation to platelet-to-lymphocyte ratio

Variable	P\L ratio (%)		Total (%)	P
	≥626	≤262		
Disease severity				
Mild	0 (0)	88 (90.72)	88 (78.5)	0.000
Moderate	4 (26.67)	9 (9.28)	13 (11.7)	
Severe	11 (73.33)	0 (0)	11 (9.8)	
Total	15 (13.4)	97 (86.60)	112 (100)	

P assessed by Fisher's exact test. P/L: Platelet-to-lymphocyte

Table 7: Platelet-to-lymphocyte ratio in patients with coronavirus disease-19 in relation to the length of hospitalization

Variable	Length of hospitalization (%)		Total (%)	P
	≤14 days	>14 days		
P/L ratio				
≤262	51 (100)	46 (75.41)	97 (86.60)	0.000
>626	0 (0.00)	15 (24.59)	15 (13.4)	
Total	51 (45.54)	61 (54.46)	112 (100)	

P assessed by Fisher's exact test. P/L: Platelet-to-lymphocyte

Table 8: Neutrophil/lymphocyte ratio in patients with coronavirus disease-19 in relation to the length of hospitalization

Variable	Length of hospitalization (%)		Total (%)	P
	≤14 days	>14 days		
N/L ratio				
<3.1	50 (98.04)	34 (55.74)	84 (75)	0.000
≥3.1	1 (1.96)	27 (44.26)	28 (25)	
Total	51 (45.54)	61 (54.46)	112 (100)	

P assessed by Fisher's exact test. N\L: Neutrophil/lymphocyte

following the local guidelines of the hospital. The overall period of stay in hospital was reported. The primary outcomes of the study were improvement or death.

Statistical analysis

Data obtained were analysed using the Statistical Package for the Social Sciences (SPSS) software version 26.0. Armonk, NY: IBM Crop. Comparisons of variables using (cross tab) and Fisher's exact test while differences between two means variables using (independent t-test). Interclasses differences of hematological parameters according to severity (more than two group) done by (One –Way ANOVA test).

Results

The demographic characteristics of patient with covid-19 as shown in table 1, revealed that females (56.25%) were more than males (43.75%) with overall mean age of 38.31 ±19.79 years (age ranged from <15 to > 70 years) half of them were between age group of 15-45 years.

Severity categorization showed that 88 (78.58%) were mild (mild group), 13 (11.60%) as moderate, and 11 (9.82%) as severe (severe group) on admission,105 (93.75%) of these patients admitted to the infectious ward and 7 (6.25%) in respiratory and ICU.

The length of the stay in hospital ranged from 10 to 35 days with a mean duration of hospital stay of 17.33 ± 5.70. Of these patients, only 5 (4.46%) died during hospitalization.

The level of serum ferritin was high (>300ng/ml) in 28.57% of patients, most of them had moderate and severe disease as compared to 12.5% of patients with low serum ferritin and all of them had mild disease as in table 2.

Neutrophil/lymphocyte ratio was ≥ 3.1 in 28 patients (25%) as shown in table 3, most of them had moderate and severe disease. The eleven patients with severe disease were all ≥ 65 years as compared 17 patients < 65 years non of them had severe disease and that was statistically significant as shown in table 4.

Fifty three (47.32%) patients were having blood group O, 96.32% of them had mild disease as compared to only 52.68% of non-O blood group patients which was statistically significant as shown in table 5.

The current study showed that PLR ≥ 626 was found in 15 patient (13.39%) as shown in table 6, non of them had mild disease as compared to 97 patients (86.6%) with PLR < 626, non of them had severe disease (*P*=0.000).

All the patients with higher PLR ≥ 626 had longer duration of hospitalization (>14 days) which is statistically significant when compared with patients had lower PLR. as in Table 7.

Almost all the patients with high NLR found to have long duration of hospitalization (>14 days) as compared to those with lower NLR and that was statistically significant (P=0.000), as in table 8.

Discussion

Nowadays, the COVID-19 outbreak has caused widespread concern and threatened the global public health security. This prospective study was designed to include all patients with covid-19, therefore it enrolled 112 PCR.-confirmed COVID19 patients admitted to infectious wards at Basra Teaching Hospital. This study showed most cases between the age group of 15 and 45 years because they are more likely to be in the workforce increasing their risk of exposure and this was parallel to other Iraqi and published data from university of Basrah[11]. Female gender was more frequently affected than male in the current study which corresponds to earlier report about COVID19 epidemiology in Basra.[12]

Severity categorization in current study showed that majority were mild, then moderate and less than 10% as severe on admission, these findings are comparable to data from epidemiological study had been conducted in Basra city.[12]

Clinicians are searching for a reliable prognostic marker that can distinguish patients at risk of developing more severe forms of the disease in order to better manage hospital resources. The NLR in peripheral blood has been studied as a systemic inflammatory marker, and various studies have shown that it is a valid prognostic factor in various solid tumors[13] and other chronic diseases such as lung, cardiovascular, and kidney diseases. In this study, we studied the NLR in relation to the disease outcome and length of hospitalization and showed patients (25%) with N/L ratio ≥3.1, of these patients (39.29%) with age ≥65 years, and all in those with severe categories (76.47%) with statically significant (P = 0.000). All patients (28) had long duration of hospitalization (>14 days) with statistically significant (P = 0.000). Our findings were consistent with those of previous studies (Yang *et al*. and Huang *et al*.) on the relationship between NLR and prognosis of many other infectious diseases.[14,15] Furthermore, the study found that 13.39% patients had higher PLR, all of them had moderate and severe disease while those (86.6%) with low PLR most of them had mild disease and non had severe disease. All patients with P/L ratio ≥ 626 had long duration of hospitalization (more than 14 days) with statically significant (P = 0.000). Our findings were consistent with the previous study of Huang *et al*.[15]

The current study revealed that leucocytosis (found in 9.82%) was associated with moderate to severe disease.

On the other hand, leukopenia (5.4%) and lymphopenia (5.4) wasfound only in patients with severe disease. Other changes in hematological parameters were neutrophilia (14.28%), thrombocytosis (6.26%) and thrombocytopenia (5.36%). The association of lymphopenia with disease severity and outcome of COVID19 was also observed in other Asian studies, however the studied population showed obviously smaller percentage as compare to 63% from Wuhan , and 42% of patients outside Wuhan [16,17] or 28% in Singapore.[18] These differences could be explained by multiethnicity and smaller number of patients in this study might be related to initial local guidelines of treatments with admission of all symptomatic patients regardless the severity , also thrombocytopenia in this study was not associated with severity of disease a thing that was not corresponding to the finding of meta analysis of Giuseppe Lippi *et al*.[19]

The high serum ferritin value was obvious and increased in our cohort in which it associated with increasing severity from mild to moderate to severe (7.15%), (11.6%), (9.82%), respectively, this finding is corresponding to what is published in another study by vergas-vergas.[20]

The limitations of the study
The study was a prospective study not followed up patients to observe the changes in these results after treatment, also lacking linking between the changes in hematological parameters and the clinical progression of the patients.

Conclusion and Recommendations

In conclusion the study found that the severity of COVID19 was associated with leukopenia, lymphopenia and elevated values of both NLR and PLR. On the other hand, both values (NLR and PLR) could be used as hematological predictors for disease severity and the outcome because these parameters are related to the length of hospitalization. These values could be quickly calculated based on a blood routine test on admission, so we should recommend routine use of these laboratory findings to identify high-risk COVID-19 patients.

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Conflicts of interest
There are no conflicts of interest.

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